WHO CHRONICLE

VOL. 15, No. 12 - DECEMBER 1961

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WORLD HEALTH ORGANIZATION

In this issue

- *A number of countries are building or planning nuclear-powered merchant ships. These vessels raise entirely new health problems, chief among them being how to dispose of radioactive waste at sea, and how to prevent the ships from endangering public health should they collide, burn, sink, or run aground (see page 442).*

- *Certain chemical compounds have been found to increase the resistance of the tissues to injury by ionizing radiation. So far, only the mercaptoamine derivatives appear to have a possible clinical application. The protective action and pharmacological properties of these compounds have been extensively studied (see page 450).*

- *Until three years ago, it was believed that kidney transplantation was possible only between identical twins. Since then a kidney has been successfully transplanted to a previously irradiated patient from his non-identical twin, and other kidney grafts in irradiated patients have persisted much longer than similar grafts in non-irradiated patients (see page 461).*

- *Although bone marrow grafts can be readily obtained in irradiated animals, attempts to treat radiation injury by bone marrow transfusions have shown that in man it is difficult to obtain a primary take. A further obstacle may be the occurrence of a possibly fatal complication known as the " secondary syndrome ", due to an immunological reaction of the graft against the host. This is a well-defined syndrome in animals and a few cases of an apparently similar reaction in man have been reported (see page 451).*

- *Man's exposure to natural radiation may be higher indoors than outside, although still far below the danger level. This is because most building materials, while shielding against external radiation, themselves contain radioactive substances. The level of exposure is least in houses built of wood and tends to be greatest in houses built of light-weight concrete containing alum shale (see page 437).*

IONIZING RADIATION AND HEALTH

The human species has always been exposed to radiation—cosmic radiation, radiation from radioactive substances in the earth's crust, and radiation from normal radioactive constituents of the human body itself. But with the discovery of X-rays and radium at the turn of the century, the advent of nuclear fission in the fourth and fifth decades of the century, and the vast increase in the number of uses to which ionizing radiation and radioactive materials are now being put, the actual and potential exposure of man has risen to such an extent as to become a subject of international concern.

In 1960 a report was prepared for the Thirteenth World Health Assembly on the hazards of radiation to health and the measures required for their prevention. This report has now been published.[1] Because man's natural exposure includes so many different kinds of radiation, the authors argue, it does not seem likely that radiation from artificial sources will cause new types of biological effect. But there are some differences between natural and artificial sources: for example, natural radiation produces chronic low-level exposure with the dose-rate varying within a rather narrow range, whereas the dose-rate from some artificial sources is much higher, even though the total dose may not be very different. About these differences and the effect they may have upon the human organism knowledge is still incomplete.

Biological effects of radiation

If living tissue is exposed to ionizing radiation, energy is transferred from the radiation to the cell molecules and cellular function may be disturbed. It is known from radiotherapy that, if the energy transferred is sufficiently great, cell destruction and tissue necrosis may follow. Different organs and tissues of the body have different sensitivities to ionizing radiations, and radiation of the whole body in doses too low to cause visible destruction of the skin may yet be lethal, because of their effect on sensitive organs within the body.

The effects of ionizing radiation may not be immediately obvious, but may appear a short or a long time after exposure. They have been held by various authorities to include genetic effects, the induction of leukaemia and other malignant neoplasms, and acceleration of the process of aging. One interesting hypothesis—the mutation hypothesis of carcinogenesis—is that radiation causes changes in the structure of the molecules of deoxyribonucleic acid (DNA) within the chromosomal material of the cell, transforming a normal cell into a malignant one. If this is so, it may be possible for one high-energy quantum of radiation and therefore even an infinitesimal dose to produce a primary cell injury of serious consequences; but the same effect could well result from chemical reaction between some critical cellular structure or structures and free radicals formed by radiation within the cell.

It is extremely difficult to obtain evidence on the effect of radiation on the process of aging; while some investigators have found that it decreases the life span in some animals, others report an increase in the life span. Reliable data about human beings are obviously even more difficult to obtain.

The production of mutations and of chromosome changes as a result of radiation has been known from 1927, but only in the fruit fly *Drosophila* and, later, in mice. Lindell & Dobson point out that:

"There is a practical barrier in the way of experimentally proving a theory of direct somatic mutation effects as the cause of late injuries on humans at low radiation levels. It can be shown that the probability

[1] Lindell, B. & Dobson, R. L. (1961) *Ionizing radiation and health*, Geneva (*World Health Organization: Public Health Papers*, No. 6).

of observable effects at radiation levels lower than those of the natural radiation is so small that the size of the population which would need to be studied to secure statistical significance would become prohibitively large. Another important factor is that all effects produced by ionizing radiation at these levels, as far as is known, also occur naturally, and can be caused by other agents such as heat, chemicals, etc. All conclusions with regard to possible radiation effects on man at such low levels are really extrapolations relying upon observations at higher dose levels, and most often on animal experiments rather than on human data. This introduces a substantial uncertainty since, generally speaking, the lowest dose-rates at which such experiments can be carried out are of a magnitude higher than the dose-rate for natural radiation. However, the uncertainty is not 'substantial' by comparison with what we know about other noxious agents in our environment, and exists only to the extent that the true risk may be smaller than the stated maximum—not larger." (p. 14)

There is also the possibility that the cell may have a very high rate of recovery when the dose to which it has been exposed is small.

The various sources of radiation produce a very wide range of dose-rates. The body is exposed to natural radiation at a fairly constant rate, amounting to about 0.1 rad [2] in a year. Some X-ray diagnostic procedures may involve exposures of this amount or more, but at higher dose-rates. Except possibly for some changes in the blood, there seems to be little evidence that high and low dose-rates produce significantly different types of biological effect, but it is possible that the capacity of radiation to produce changes in tissue varies with the dose-rates. The biological effect of ionizing radiation does vary with the ionization density of the radiation, and a special weighting factor has been designed to take this variation into account. This RBE (radiobiological effectiveness) factor varies with the type and degree of biological effect, dose-rate, dose fractionation, oxygen tension, pH, and temperature.

There are also some biological factors that must be considered in the study of radiation exposure. As it is believed that some radiation injuries do not become manifest until many years after exposure, an important parameter is the expectation of life at the time of exposure. Another, in an assessment of the genetic significance of radiation doses to the gonads, is whether the individual exposed is likely to have children in the future. Others still are the localization of the dose in the body if the whole body has not been exposed, and the age, sex, and general health of the person exposed.

As long as the true relationship between radiation dose and biological effect is not known, it is impossible to compare the exposure of a few individuals to moderate or high doses of radiation with that of a large number of persons to low levels. If there is no threshold before an effect occurs and the dose-effect relation is linear through the origin (and if all recovery can be neglected), the *average* dose in a population, as derived from properly weighted individual doses, would be the relevant one. If, on the other hand, there is a threshold, only a fraction of the exposures will have relevance, and the significant doses will be the *individual* ones.

Sources of radiation

Lindell & Dobson subject the sources of ionizing radiation to which man is exposed to close scrutiny. The first of these, and the one to which man has been exposed throughout his entire evolution, is natural radiation.

Natural radiation

The quality of the various components of natural radiation—cosmic rays, radioactive elements in the earth's crust, radioisotopes within the body—is such that the biological effects of each would be about the same for the same dose, except for alpha rays, of greater energy and ionization density, which are derived from radium within the body and chiefly affect the cells in and adjacent to bone because ingested radium is preferentially taken up by the skeleton. The amount of natural radiation to which people are exposed varies considerably from place to place with latitude, altitude, and environment, but no ill effects have yet been observed to result from these variations.

[2] One rad equals an energy dissipation of 100 ergs per gram of the exposed tissue.

Man's exposure to natural radiation is modified by a number of factors. One of these is the kind of house in which he lives. Indoor exposure is often higher than outdoor because most building materials heavy enough to absorb and reduce cosmic radiation also contain natural radioactive substances that more than counterbalance the shielding effects of the building. Terrestrial gamma radiation is least in houses built of wood, and tends to be most in houses built of light-weight concrete containing alum shale, with houses built of brick coming between; and the annual dose to the lungs from radon and thoron in the air is similarly less in wooden houses. Again, in a ship at sea the terrestrial component is absent, so that the amount of radiation received is only about half that received on land. On the other hand, the amount received in an aeroplane at extremely high altitudes is increased because of the increase in the cosmic ray component.

Medical exposure

Medical procedures make a striking contribution to man's exposure to radiation. The genetically significant dose from X-ray diagnostic procedures appears to range from 17% to 160% of the average dose from natural radiation, and the dose to other soft tissues is probably of the same order. The significance of the dose to some of the tissues is not clear, as it depends on whether there is a threshold in the dose-effect relation, which is not known. Moreover, it has often been assumed that the dose of radiation given to the active bone marrow is related to the induction of leukaemia; but it is not known whether this dose is the maximum dose in some portion of the marrow or the mean dose over the whole mass of the active marrow, or, for that matter, whether exposure of other tissues is involved.

As far as can be calculated, the average doses of radiation (meaning the genetically significant doses) from medical exposure in the more developed countries seem to be of the same order of magnitude as the average dose from natural radiation. The contribution made by radioisotopes to the genetically significant dose received by man, however, is negligible at the present time. Radiotherapy does not contribute significantly to the genetic dose received by the population because the number of patients is small, and it is in a different category. To begin with, the patient's expectation of life is often less than normal because of the disease for which he is being given radiotherapy. The dose of radiation given to some portion of the body may be several times higher than that given in any diagnostic procedure. The aim of good therapeutic practice in cancer is to reduce the number of patients who die from their disease because the radiation dose is insufficient and the number who die because the dose causes severe radiation injury. This aim is pursued by increasing refinement of technique and equipment.

Occupational exposure

Most countries apply radiation protection principles based on those formulated by the International Commission on Radiological Protection, and have elaborated regulations and safety codes laying down maximum permissible levels for exposure. In medical and industrial work, radiation injuries are mainly caused by inexperience, lack of precise instructions, or carelessness, one of the difficulties in radiation protection work being that radiation cannot be detected by any of the senses, so that carelessness may not be immediately corrected. Moreover, biological effects—even to the extent of necrosis of the skin—may not become manifest till after some time. Hence the danger in atomic installations. In many of these installations normal exposure levels are lower than for other radiation work because of the care taken in protection and in educating the worker. But the potential risk is great, much greater than in hospitals, for instance, and several fatal accidents have occurred. Also, of course, the number of people engaged in atomic energy work is increasing steadily, and the number of accidents is liable to increase too. Nevertheless, the contribution from occupational exposure to the average population exposure burden is quite small.

Exposure in everyday life

The extent to which man is exposed to radiation in everyday life is difficult to assess. At present it seems to be small, but it will probably increase in the future unless more care is taken. One of the most common sources of radiation is the luminous watch dial; here, although the dose is small, the range of radioactivity is wide. Some radiation occurs in television receivers, but is usually screened off. In some countries X-ray fluoroscopy is used for fitting shoes. Luminous paints containing radium frequently appear on the market; radioactive brushes are sometimes used to remove the dust from photographic films and gramophone records; and so on.

Other sources

Two other sources that are much in the news at present and are receiving considerable international attention are radioactive waste from atomic energy installations, hospitals, laboratories, etc., and radioactive fall-out from nuclear test explosions. The contribution of radioactive waste to total exposure of the population appears to be insignificant at present; but the problem of its disposal is of vital importance for the future. Radioactive fall-out is a special problem and has been intensively studied. It is significant that dosages from fall-out have been very small compared to those due to natural radiation. The above-ground testing of nuclear devices produces local fall-out of radioactive material, followed by world-wide fall-out from the stratosphere. The fission products constitute a greater biological problem than the simultaneously induced radioactivity or the residual fissionable material, the atmosphere possibly being contaminated for years, the fall-out reaching plants and animals and therefore man, both directly and indirectly by his ingestion of contaminated plants or animal meat.

Much remains to be learnt about radioactive fall-out, as indeed about radiation generally. As far as is known, the dose-rates are small compared to the variations from place to place in natural radiation. The radiation quality is the same, but fission products contain some rare elements whose significance to living organisms is not fully understood.

RADIATION PROTECTION

The protection of mankind from ionizing radiation was discussed at the Thirteenth World Health Assembly in 1960, and it was resolved, inter alia, *that national health authorities should be encouraged and assisted by WHO to recognize the importance of the role they should play and increase their activities in this field. The Director-General was asked to report to the Fourteenth World Health Assembly on progress in developing and staffing radiation control programmes, with particular reference to the responsibility of national health authorities and WHO.*

In his report on radiation protection to the Fourteenth World Health Assembly the Director-General of WHO outlined the development of measures in this field.

The beginnings

Röntgen discovered X-rays in 1895. The Curies discovered radium in 1898. Very soon afterwards it was found that ionizing radiations could be harmful. However, the number of people involved was small, most of them being technical workers using X-rays or radium, and in the 1920's and 1930's it was considered that the problem of protection from radiation could be largely solved by recommendations of national radiation protection committees. In addition, a series of recommendations were made by the Inter-

national Commission on Radiological Protection from 1928 onwards. In many countries specialized laboratories helped to bring these recommendations to the notice of those concerned. In Sweden in 1925, Sievert offered the services of the Institute of Radiophysics as a laboratory to help in protection measures. In 1941, an act was passed in Sweden requiring the licensing and inspection of all radiation installations, much of the responsibility for this being delegated to the Institute of Radiophysics. Many other countries had similar radiation control programmes, but on a voluntary basis.

Another type of hazard appeared after the First World War, when a great deal of radium-containing paint began to be used for making luminous dials on watches, clocks, etc. This was considered as an industrial health problem, and legislation for the control of luminizing work was passed.

The introduction of atomic energy

During and after the Second World War atomic energy installations came into being. In some countries this led to atomic energy commissions being given certain very specific responsibilities for preventing health from being endangered by their operations. With the advent of atomic energy, radiation protection became a very much more complex problem. Whereas previously five or ten curies of radium had been the maximum in any one unit, atomic reactors contained hundreds of thousands of curies of radioactivity or more. Also, health hazards such as those associated with the neutron, which had previously been confined to a few nuclear physics laboratories, became of wider importance. New radioactive substances were produced. Some were fission products resulting from fission of uranium or plutonium, others were artificial elements heavier than uranium, and still others were radioisotopes produced by cyclotrons or by irradiation in atomic reactors. The International Commission on Radiological Protection now recommends maximum permissible concentrations for over 240 different radioisotopes.

The sudden introduction of so many new isotopes and particles stimulated radiobiological research. Although radiobiology was already a relatively flourishing subject, most work had been done on radiotherapeutic levels of doses; now an attempt was made to discover effects at, or not much above, maximum permissible levels. This research did much to refine knowledge of radiation hazards and led to a lowering of recommended maximum permissible levels.

Since atomic energy organizations were governmental agencies in most countries, at first little legislation was felt to be required, apart from that establishing the atomic energy organizations themselves. But as a by-product of atomic energy, a growing number of radioisotopes began to be sold on the open market, and among the first radiation protection problems arising outside atomic energy organizations were those associated with the medical use of radioisotopes. Above a certain level the use of these radioisotopes could be harmful, as could their unsuitable therapeutic use. In many countries, this problem was solved more or less successfully by making an informal agreement with the relatively few sources of supply that radioisotopes should be supplied to doctors only through committees of medical experts. In other countries, e.g., Australia, the situation was controlled by legislation.

Radioisotopes were also being more and more employed in industry. Comparatively large sources of radiation were often used for radiographs of metal to show welding or other faults, while small sources were used for such devices as thickness gauges or static eliminators; and conventional X-rays were also being employed. Factory legislation on radiation protection is now beginning to be introduced, particularly for enclosed sources of radiation but also for open sources, i.e., sources that might produce a radioactive inhalation hazard. The International Labour Office and the International Atomic Energy Agency (IAEA) have both produced model codes of regulations on radiation protection in their respective fields.

Transport of isotopes was and still is carried on a great deal by air; the Inter-

national Air Transport Association was a pioneer in the introduction of international recommendations on this subject. As larger and larger sources are being transported by road or rail, governments appear also to be considering legislation on transport by this means. IAEA, with WHO representation, has recently developed a code on the transport of radioisotopes in general.

A new development is the operation of reactors by nationalized or private industry. This has been felt in most countries to necessitate legislation instituting a system of reactor licensing; licences are granted when the responsible authority is satisfied that the site chosen is suitable and that operating conditions will meet certain specific criteria of health and safety.

Control of radioactive waste has always been a source of worry for public health authorities, involving as it does large atomic energy installations, factories, mines, small laboratories, and, recently, nuclear-powered shipping.[1] Moreover, such waste may affect the land, the sea, fresh water, or the air, and food destined for human consumption may be contaminated. Legislation on this subject is now being introduced in some countries, and may specify the registration of sources of production of waste. Control of waste is dependent on facilities for radioactive measurement, and these have been provided by some public health authorities. Gross counting of radioactivity from a mixture of isotopes is seldom completely adequate for this purpose, since different radioisotopes have very different maximum permissible concentrations. Therefore laboratories where radioactive isotopes can be separated by radiochemistry and counted individually may be necessary.

The fall-out from nuclear tests has stimulated some countries to undertake the analysis of food and water to discover their content of radioactive material and to estimate the total intake into the body of the longer-lived isotopes, strontium-90 and caesium-137. This research has required a large number of radiochemical analyses, since analysis of one source only, e.g., water, sheds very little light upon the whole picture. The estimates have been checked by analysing human bones obtained at post-mortem examinations for strontium-90, and the results have been discussed by the United Nations Scientific Committee on the Effects of Atomic Radiation (at which WHO is represented) and by FAO.

With the stress now laid on scientific education, simple experiments using radioisotopes are often performed in schools, and some form of control may be introduced to enable such experiments to be performed safely. Even toys occasionally have luminous paint applied to them and may have to be controlled in some way. Another potential hazard to children is the use of X-ray apparatus to assist in shoe fitting. Operators of such apparatus, in the past at least, may also have received considerable doses of radiation. Some countries have forbidden the use of this apparatus, while others have exerted some form of control by specifying the degree of shielding, etc. required.

Increased interest in the medical use of X-rays

Committees of inquiry into radiation hazards appear to have been somewhat surprised to discover that by far the highest contribution to the average population dose of radiation comes from the medical use of X-rays, particularly in diagnostic radiology. This applies especially, of course, to those countries with well-developed medical services. The genetic risk has been perhaps particularly in the mind of investigating committees, and doses from X-rays in this connexion are usually expressed as the average dose to the gonads of a national population as a whole, or, with corrections, as the genetically significant dose.

It is interesting to trace the history of opinion on the genetic risk of radiation. Muller discovered the genetic effect of radiation on insects in 1927, but it was not until large-scale research had demonstrated that the effect was considerably greater in mammals (mice) that much attention was paid to the risk. Nor was it realized at first how extensively the use of diagnostic radia-

[1] See article on p. 442.

tion had spread in many countries, and that it might accordingly have an appreciable genetic effect on the population as a whole. It is not, however, possible to express this risk in terms of human hereditary disease with any degree of accuracy until more is known about human genetics.

Another, entirely different, way of expressing the average dose of X-radiation to a population is by estimating the mean dose to the red marrow (i.e., the haemopoietic tissue). This is calculated on the assumption that X-ray doses may have significance in the production of leukaemia (even though a positive correlation has been obtained only at much higher levels of radiation than are attained in the normal diagnostic use of X-rays).

Much can be done to reduce the total dose and the gonad dose from the diagnostic use of X-rays. Reduction can be achieved by adequate filtration, proper coning procedures, and the improvement of techniques through the use of higher kilovoltage and lower milliamperage.

As a step towards protection of radiographers and radiologists, there has been a remarkable increase over the last few years in the use of film badges to measure individual doses of radiation. It is always found that when an individual's dose is known, he or she takes pride in reducing it; it can therefore be said that measurement leads to greater care in protection. A few countries have set up committees to reappraise the use of radiotherapy and mass radiography in medical care in the light of the new knowledge about radiation hazards obtained in the last few years.

Organization of protective measures

It may be pertinent here to consider various general features in the organization and control of radiation hazards; such general features, as seen by one country, are discussed in a handbook published by the United States National Bureau of Standards.[2] In several countries the law requires the licensing or control of all sources of ionizing radiation, including medical X-ray apparatus; much of this legislation dates back many years.

Various factors must be taken into account when comparing legislative procedures in different countries. A country with many federated states will choose different procedures from one in which the government is centralized. The size of the country may also be important; for instance, in some states one laboratory serves the whole country, whereas others, such as France, may choose to set up regional laboratories. The degree of industrialization and development of medical care must also be taken into account.

One of the most useful radiation control methods still appears to be an advisory laboratory or laboratories where film badges are processed and where, if necessary, more advanced services and facilities such as radiochemical analysis and whole body counters may be provided. Examples of such institutions are the Radiological Protection Service in the United Kingdom, or, on a more regional basis, the sanitary and epidemiological stations of the USSR. It must be stressed that even film-badge services require qualified technicians to develop the films and interpret the results. It is also common practice to have an advisory body of senior radiation experts from all parts of a country to advise the central health authority on problems as they arise. Government-sponsored codes of practice for detailed radiation protection measures in particular sets of circumstances have been established by many countries, including the United Kingdom,[3] the USA,[2] and the USSR.[4]

As regards legislation, certain general points may be made. One of the first difficulties in many countries is the shortage of trained personnel. It is of little avail to enact elaborate legislation if the inspectors enforcing the law are inadequate; poorly

[2] US National Committee on Radiation Protection (1955) *Regulation of radiation exposure by legislative means*, Washington, D.C. (National Bureau of Standards Handbook 61).

[3] Great Britain, Standing Advisory Committee to Advise Ministers under the Radioactive Substances Act (1957) *Code of practice for the protection of persons exposed to ionizing radiations*, London.

[4] USSR Ministry of Health (1958) [*Measures for the protection of persons engaged in work with radioactive substances*], Moscow.

trained inspectors can quickly bring the law into disrepute. WHO has always emphasized the importance of training in its programmes, and has organized different types of radiation protection courses as well as awarding individual fellowships. The starting point of legislation (as suggested in the United States handbook mentioned above) may be the registration of radiation sources, although the more complicated system of licensing may be applicable in some countries. It is often convenient to have a general act on radiation protection, and more specific regulations containing the technical details. Thus, the act can be implemented gradually as technical personnel become available. Moreover, radiation protection standards are still in a fluid stage and may be changed as more research work is carried out. Technical details in regulations under a main act may be more easily revised to operate under new maximum permissible levels or with new types of measuring apparatus. It is often convenient to distinguish between minor and major sources of radiation so that legislation will not concentrate too much on minor sources and devote relatively little attention to major sources. This often leads to a list of exemptions from the full procedure established for major sources.

Member States have adopted a very wide variety of methods for controlling health hazards from ionizing radiation. Official texts on the subject are sometimes precatory, sometimes mandatory, and the implementation of the laws falls sometimes to a body constituted specially for this purpose, sometimes to a single already existing government department, such as the Ministry of Health, and sometimes to several distinct authorities.

HEALTH HAZARDS FROM NUCLEAR-POWERED MERCHANT SHIPS

An aspect of radiation protection that is likely to receive increasing attention is the danger to health from nuclear-powered ships. At present this danger is slight, since such ships are few; but many more will be built in the near future. The following article is based on a report on the subject submitted by the Director-General of WHO to the Fourteenth World Health Assembly.

Almost all nations with a major shipbuilding industry are building or planning nuclear-powered ships. A Russian atomic-powered ice-breaker, the *Lenin*, is in operation, and the US nuclear merchant ship N.S. *Savannah* will shortly become operational. The principal economic advantages of nuclear propulsion in ships are greatly increased range without refuelling and potentially greater cargo-carrying capacity. These advantages are offset, at present, by the high cost of construction and operation, but it seems likely that in time nuclear propulsion will become economically competitive.

The radioactive hazards from nuclear ships have been under discussion in recent years, and several extensive studies have been undertaken on them. The problems are three in number: first, that of dealing with radioactive waste disposal into the sea from nuclear merchant ships; second, that of laying down standards of safety of construction to prevent these ships from becoming a public health hazard in the event of accident; third, that of possible hazards to the crew and maintenance workers. Only the first two problems need discussion, since radiation protection measures for the crews of nuclear merchant ships will be very similar to those for land-based atomic energy installations. It should be said, however, that at the Forty-First (Maritime) Session of the International Labour Conference in 1958, a resolution was passed requesting the International Labour

Office to study this problem in relation to ships' crews. The United Nations specialized agencies have been active as a whole in this field.

In a nuclear-powered ship the reactor replaces the conventional boilers fired by oil or coal. The primary coolant of the reactor, usually water under pressure, heats water in a secondary non-radioactive system by means of a heat exchanger, thus raising steam to drive turbines in the usual way. The vast bulk of the radioactive fission products formed inside the reactors of nuclear ships are removed with the spent fuel elements and processed on land. These fission products are then dealt with in the customary manner for the disposal of such wastes in the country concerned, i.e., mainly by storage in stainless steel tanks. There are, however, relatively small amounts of radioactive waste that may be produced during the normal operation of a nuclear ship, and it might be possible to discharge some or all of this waste into the sea under suitable conditions, or, in some cases, to store it temporarily in tanks on the ship. This waste may be derived: (*a*) from the expansion volume of primary coolant during the warming up of a pressurized water reactor; (*b*) from operational leakage from various components of the primary and auxiliary systems, from the laboratory, from sampling, from equipment decontamination, and from the shower and laundry; (*c*) from ion exchange resins that remove corrosion products from the primary coolant; and (*d*) possibly from contaminated solid materials.[1]

Liquid effluent may contain low concentrations of radioactive corrosion products together with low concentrations of fission products. The ion exchange resins will contain the same materials at considerably higher activities. From consideration of the diluting powers of the ocean and of the concentration of radioisotopes by fish and other marine organisms that may be eaten by man, the US National Academy of Sciences [1] has made certain recommendations about the disposal of radioactive waste from nuclear-powered ships. It should be remembered that these ships are not, like most atomic installations, static and that, unlike other ships, they cannot discharge their waste into the sea anywhere or almost anywhere.

[1] National Academy of Sciences, National Research Council (1959) *Considerations on the disposal of radioactive wastes from nuclear-powered ships into the marine environment*, Washington, D.C.

Radioactive waste disposal into the sea

The disposal of radioactive waste into the sea is a general question of which the disposal of waste from nuclear ships is only a part. Some years ago this general question was discussed by the United Nations Scientific Committee on the Effect of Atomic Radiation. FAO, UNESCO and WHO contributed a combined paper on the subject. The Committee reported in 1958 that it had " not given any detailed consideration to the technical aspects of the problem, but from information available it is clear that there is no general population hazard from this cause at the present time ". No specific mention was made of nuclear ships.

In 1958 a United Nations Conference on the Law of the Sea was held and a recommendation was made " . . . that the International Atomic Energy Agency, in consultation with existing groups and established organs having acknowledged competence in the field of radiological protection, should pursue whatever studies and take whatever action necessary to assist States in controlling the discharge or release of radioactive materials to the sea, promulgating standards, and in drawing up internationally acceptable regulations to prevent pollution of the sea by radioactive materials in amounts which would adversely affect man and his marine resources ".

IAEA, therefore, convened in October 1958 an *ad hoc* panel on radioactive waste disposal into the sea, which included in its report a section concerning nuclear ships. IAEA and UNESCO, with the co-operation of FAO, sponsored a Scientific Conference on the Disposal of Radioactive Waste (Monaco, 1959) which discussed the problem as a whole.[2] WHO has included radioactive waste disposal as a general subject in several

[2] International Atomic Energy Agency (1959) *Disposal of radioactive waste*, Vienna.

radiation protection courses and in a specific course held last year at Saclay near Paris. Very recently IAEA and the Inter-Governmental Maritime Consultative Organization (IMCO) held a symposium at Taormina on nuclear ship propulsion, with special reference to nuclear safety. The symposium was concerned with engineering matters rather than the effects of radiation on health.

Standards of safety for nuclear-powered ships

It may be said that basically the problem of controlling the hazards from land-based and ship reactors is the same—that of preventing really dangerous levels of release of fission products. It should be stated in this connexion that the safety record of the nuclear industry as a whole has been extremely good. However, there are additional problems with ship reactors due to the marine environment and the possibilities of collision, burning, sinking, or running aground.

In 1960 IMCO convened an International Conference on Safety of Life at Sea. This Conference amended the International Convention for the Safety of Life at Sea and for the first time included regulations on nuclear ships. The Conference "avoided putting into the Convention technical requirements which might hamper the development of such a new type of ship". It made some non-mandatory recommendations applicable to nuclear ships, intended to provide guidance for governments in the application of the regulations included in the Convention itself and to point out the main problems requiring attention at the present stage of technical development.

IAEA and the Government of Belgium acted as joint sponsors of the question of the liability of operators of nuclear ships at the Diplomatic Conference on Maritime Law held in Brussels in April 1961. The report of the panel of experts [3] invited by IAEA to examine the situation and to formulate conclusions and recommendations emphasized the need for continuing scientific study of the difficult technical questions encountered in the discussion of the legal issues of liability.

* * *

To sum up, it would seem fair to say that the question of health hazards from nuclear-powered ships has received considerable recognition from international bodies; however, the problem is new and highly complex, and presents many variables of which understanding is at present incomplete. To quote the US National Academy of Sciences.[4] "Greater research efforts are needed, both at sea and in the laboratory. At sea, studies should be made of extramarine and coastal environments, of circulation and mixing in the deep ocean, and of the physical and biological processes by which materials introduced into deep water may be transferred to the surface layers or removed by sedimentation. The biological half-lives of radioisotopes in marine organisms, the pathways of accumulation through the food chain, and sedimentary exchange processes need to be studied, both in the laboratory and at sea. It is obvious that these studies are of more than local or national concern, and especially those concerned with the open ocean should be undertaken jointly by all maritime nations."

[3] International Atomic Energy Agency (1960) *Liability of operators of nuclear ships*, Vienna.

[4] National Academy of Sciences, National Research Council (1960) *The biological effects of atomic radiation*, Washington, D.C.

ACCIDENTAL RADIATION INJURY

Studies of the effects of ionizing radiations in animals are of limited value for human medicine as the results cannot be reliably extrapolated to man. It is therefore essential to extract the maximum amount of information from the relatively few observations on persons accidentally exposed to high doses of radiation and those deliberately irradiated under medical supervision for therapeutic purposes. With this aim in view, IAEA and WHO, which have a common interest in radiation medicine, jointly sponsored a Scientific Meeting bringing together three groups of scientists: those with experience in the treatment of persons accidentally exposed to high doses of radiation; those employing large doses of whole-body irradiation for therapeutic purposes; and those working on related problems in experimental animals. The article below discusses some of the work relating to accidental radiation injury; the therapeutic applications of whole-body irradiation are reviewed in the article on p. 461.

The use of potent poisons in the treatment of disease is as old as the art of medicine, and every surgeon inflicts deliberate injury on the body in his attempts to correct dysfunction or repair a lesion. No other destructive agent, however, is as protean in its manifestations or as manifold in its potentialities as ionizing radiation. Unperceived by any of the senses, a high dose of ionizing radiation will destroy haemopoietic function and wreck the biochemistry of the body in a fraction of a second; the consequences may be rapidly fatal, or there may be severe illness with eventual recovery; at lower dose levels, the effects may be insidious, developing slowly over months or years, or even passed on to subsequent generations. Yet the same radiations, administered under controlled conditions, have not only become indispensable aids to diagnosis but have also been used to perform " operations " too delicate for the surgeon's knife, to arrest neoplastic diseases intractable to other therapy, and to make possible the transplantation of homologous tissues, with all the tremendous applications that this conjures up.

With the exception of the diagnostic applications, all the medical uses of ionizing radiations depend upon their destructive effects in the body. Thus a Scientific Meeting held last year to discuss the diagnosis and treatment of acute radiation injury was concerned as much with injury produced by deliberate irradiation for therapeutic purposes (see p. 461) as with the grosser type of injury produced by radiation accidents. The Meeting, sponsored jointly by IAEA and WHO, was held in Geneva from 17-21 October 1960.[1] It was attended by 30 scientists from France, India, the Netherlands, Poland, the United Kingdom, the USA, the USSR, and Yugoslavia, and 21 papers were presented. The collected papers, together with summaries of the discussions, have now been published by WHO.[2]

Many of the problems discussed at the Meeting were of a highly technical nature and of interest only to those directly concerned with the treatment of acute radiation injury. In this article and the one ou p. 461 attention is concentrated mainly on the clinical aspects of interest to the general physician and the public health worker.

The Los Alamos radiation accidents

Among the most dramatic of the papers presented at the Meeting were those containing case histories of patients accidentally exposed to high doses of irradiation. Six

[1] See *WHO Chronicle*, 1961, 15, 33.

[2] *Diagnosis and treatment of acute radiation injury*, Geneva, World Health Organization, 1961.

such accidents were described—one at a military installation in Lockport, New York, one at the Y-12 plant in Oak Ridge, Tennessee, three at the Los Alamos Scientific Laboratory, and one at Vinča, Yugoslavia. These accidents occurred mostly through ignorance of certain hazards or through the fortuitous conjunction of several unrelated factors, rather than through neglect of the prescribed precautions. With increasing experience the risks of such accidents can be reduced, but they can never be completely eliminated; hence the importance of improved methods of diagnosing and treating acute radiation injury.

The heaviest exposure occurred in the third Los Alamos accident, which took place in December 1958 during the recovery of plutonium from liquid wastes. The dose was several times greater than in any other reported accident, but fortunately only one operator was in the room at the time. Less than 30 seconds after the critical excursion —later estimated to have involved a burst of 1.5×10^7 fissions—he was found standing outside, ataxic and disoriented. His face was flushed and he kept repeating "I'm burning up, I'm burning up." Twenty-five minutes later he was admitted to hospital in a state of shock, with a blood pressure of 80/40 and a pulse rate of 160 per minute. He was extremely restless and had to be restrained by nurses, but became quieter after an injection of meperidine hydrochloride. An intravenous infusion of dextrose and calcium gluconate was started and he was later given plasma and placed in an oxygen tent. The administration of intravenous fluids and pressor drugs had to be kept up continuously, otherwise the blood pressure dropped alarmingly.

About 5 hours after the accident, he was rational, comfortable, and appeared emotionally at ease. By this time, however, dosimetry studies and blood counts had already indicated the severity of his exposure. Within 6 hours, the lymphocytes had virtually disappeared from the circulating blood, which was regarded as a very grave prognostic sign. Urinary retention was extreme: during the 36 hours between the accident and his death his total urinary output was less than 600 ml and only 3 ml of urine were found in the bladder at autopsy, in spite of a fluid intake of approximately 14 litres. However, his clinical condition remained relatively satisfactory until about 30 hours after the accident, when it deteriorated rather abruptly. He developed severe abdominal cramps and his restlessness became so great that he could not be controlled even with heavy sedation. Finally, he lapsed into a coma from which he never roused.

The dosimetry studies indicated that the combined neutron and gamma dose to the patient's anterior chest wall, and thus to the right side of the heart and anterior wall of the stomach, was approximately 12 000 rad, while the dose to the lower legs was probably less than 1000 rad. At autopsy, practically all the tissues except the lungs were found to be water-logged, and the general picture was characteristic of acute right heart failure from right-sided myocarditis. Although there were undoubtedly several contributory causes of death, the most vital injury was thus to the heart, which received the highest dose of radiation. Whether the injury was a direct effect of the radiation or toxic damage from the products of histolysis of the body as a whole is difficult to say.

The other two Los Alamos accidents occurred in 1945 and 1946 during experiments with critical assemblies consisting of a fissile core surrounded by a shield. Exposures were much less severe than in the 1958 accident, although in each case the operator conducting the experiment, who was touching the shield, was fatally injured. Both of them developed very severe and extensive radiation burns on the hands and arms which are believed to have been exposed to several thousand roentgens (r) of neutron and gamma radiation. The estimated average body doses were 840 rem [3] and 2000 rem of soft radiation (X-ray equivalent of the neutron dose) and approximately 500 r and 150 r of gamma radiation. The first patient died 25 days, the second 9 days after exposure.

[3] Abbreviation for "roentgen equivalent man", the unit of dose of ionizing radiation weighted for relative biological effectiveness.

During this time the temperature, pulse and respiratory rate steadily increased. Treatment of these patients was purely symptomatic. In the second case, both arms were packed in ice; this relieved the pain and stopped the progress of the epidermolytic process. Repeated transfusions of whole blood and plasma were also given, and medication with penicillin. Blood counts were typical of severe radiation injury, with a prompt and profound fall in the lymphocyte counts and an initial rise in the total white cell count followed by a fall.

At autopsy, one patient was found to have extreme fibrinous pericarditis, whereas the other had no evidence of inflammatory or degenerative lesions of the pericardium or myocardium, although petechial haemorrhages were present on the surface of the heart. In the latter patient, the intestines showed severe damage.

At the other end of the scale from these two fatally injured operators was a man estimated to have received an average body dose of 210 rem of soft radiation and 19 r of gamma radiation. A very vigorous man of 54, he had no symptoms at any time, although his blood counts were somewhat abnormal for two years. Another man, who had an intermediate exposure, developed fever and somnolence with typical blood changes, but could be discharged from hospital after 15 days. For the next 10 weeks, however, he spent most of his time in bed because of extreme lassitude and weakness. Gradually, he recovered his strength completely and was able to lead an active normal life.

The Lockport incident

Exposure of a very different type occurred at the military installation at Lockport in March 1960 during the replacement of a defective radar transmitter tube. Attempts were made to tune the new tube without the shield in place, under the erroneous impression that as long as no radiofrequency was produced no radiation of any type would be present. In fact, however, there was an intermittent emission of X-rays at about 150 kV for a total time of 7.2 seconds per hour. Altogether nine men were involved, of whom three were almost in contact with the tube for 20-30 minutes. Four others were working within 6 feet (180 cm) of the tube over a period of 1-2 hours. The other two were more than 8 feet (240 cm) from the tube and received only slight exposures. It was later estimated that the most seriously injured casualty might have received as much as 1200-1500 r to certain areas of the body, particularly the right side of the head, right arm and axilla. While still subject to exposure and unaware of the danger, the men noticed severe headache, " deep " within the centre of the head. In those most seriously injured, this was soon followed by nausea and vomiting. All the men were admitted to hospital 2-4 days after exposure. They were placed in bacteriologically clean rooms and strict contagion precautions were observed, but it was decided to reserve antibiotics and blood transfusions for actual infections or severe bleeding, and treatment was conservative throughout.

The most persistent symptoms were nausea and lassitude. Erythema developed in all the patients, as well as dryness of the mucous membranes; conjunctival reddening was present in all except one. In the most severely injured patient, swelling of the tongue and lips developed on the 7th day, with severe glossitis and stomatitis. These lesions lasted about a week. Loss of hair began on the 13th day and progressed to complete alopecia (see Fig. 6, p. 455). On the 44th day, the patient became febrile, extremely somnolent and moderately ataxic. The somnolence persisted for 8-10 days and neurological symptoms, including transient paresthesias, for 12 days. Other changes noted included pitting oedema persisting until 5½ months after exposure, myxoedema-like appearance, and retinal haemorrhages and exudates associated with diminution of vision. The total white cell count fell progressively until the 6th week after exposure, and lymphopenia was severe; haemoglobin and haematocrit values fell only slightly, but a reticulocytosis gradually developed. All blood findings had returned to normal approximately 4 months after exposure.

The Y-12 and Vinča accidents

Although these two accidents came about in different circumstances, the nature of the exposure was quite similar and a number of comparative studies have been made. The Y-12 accident occurred when enriched uranium was allowed to drain into a drum intended to contain only water; the Vinča accident was the result of a power increase during an experiment with a zero-energy reactor which was supposed to be operating at subcritical levels. In both cases, several operators were exposed to fairly high levels of mixed gamma and neutron radiation. Studies based on the conversion of sodium-23 to sodium-24 in the body indicated that the five men most heavily exposed in the Y-12 accident received doses of 236-365 rad, whereas in the Vinča accident the range for five of the six exposed men was 323-436 rad (the sixth man received only 207 rad). These retrospective dose estimates are naturally subject to many sources of error, but the clinical findings confirm that the Vinča patients had been exposed to a higher total dose than those at Oak Ridge. All patients had nausea and vomiting, but in the Vinča patients these symptoms developed earlier and were more severe; the most heavily irradiated patient also had diarrhoea. Loss of hair was common to both sets of patients, but whereas marked baldness occurred in only two of the five Y-12 patients and was confined to an area over the occiput, four of the six Vinča patients developed almost complete alopecia. From the 3rd day after the accident, all the Y-12 patients were in generally good condition and none of them displayed alarming signs or symptoms. Specific infections in two of them were controlled with tetracycline, but the others received nothing more than an occasional dose of aspirin or sedative. On the other hand, all except one of the Vinča patients presented an alarming picture from the 4th to the 7th week. They became febrile and passed into a typhoid-like state; anorexia and vomiting reappeared, night sweating was profuse, and urine output diminished. In addition, there were abdominal pains and gingival haemorrhages. The most severely injured patient developed intestinal bleeding and massive haemoptyses, which finally led to his death.

After being given antishock treatment and antibiotics, the Vinča patients were transferred to the Curie Foundation (Hôpital Curie) in Paris for further observation and treatment. There they were kept in isolation, with aseptic and antiseptic precautions, and ordered complete rest. Special diets were given, supplemented by vitamins, aminoacids and liver and adrenocortical extracts. Massive platelet transfusions were given to combat haemorrhages in three patients. In view of the continued deterioration in the patients' condition, it was decided to attempt a transfusion of haemopoietic tissue. In the most seriously injured patient, a transfusion of foetal haemopoietic tissue, taken from the spleen and liver of a premature infant a few minutes after death, elicited no response. Adult bone marrow was therefore administered. In four of the patients, there was a remarkable improvement in the clinical condition, with a return to normal of the temperature, disappearance of the typhoid state, improvement in appetite and gain in weight. At the same time, the blood counts, which had indicated almost total bone marrow aplasia, began to increase. In the most severely injured patient, although there was a rapid rise in the blood count, the intestinal, pulmonary and renal complications increased in severity and led to a fatal outcome. Three months after the marrow was given, the clinical and haematological condition of all the remaining patients was satisfactory and they were transferred back to Belgrade. It is of particular interest that the one patient who was not given marrow recovered more slowly than the others, although he had received a smaller dose of irradiation and had been much less seriously ill. Follow-up studies on these five patients showed that although the haematological and biochemical findings had returned to normal, slight asthenia, fatiguability and facial pallor were still present 2 years after the accident. Two of the patients complained of nausea and inability to eat heavy food. The one female patient suffered from dysmenorrhoea and poly-

menorrhoea, and two of the men had azoospermia or hypospermia.

Assessment of radiation injury

Detailed case histories of radiation casualties are of immense value because at present the most satisfactory way of assessing the severity of radiation injury is by comparing the course of the illness with that in patients previously studied. As already indicated, it is extremely difficult to make accurate estimates of the doses to which accident victims have been exposed. Moreover, it is important to know not only the total tissue dose in rad, but also the gamma-ray/neutron dose ratio and the neutron spectrum, since the fast neutrons produce different effects from the slower, thermal neutrons which are more easily captured by atomic nuclei. Another complication is that in radiation accidents the dose is usually distributed very unevenly over the body, some parts of which may be shielded and receive only a small fraction of the dose delivered to others. Finally, there are indications that the severity of the injury may depend partly on the dose-rate, at least in some circumstances.

For these reasons, the interpretation of dosimetry measurements is at present fraught with grave difficulties. Attempts have been made to find biological dosimeters, that is, physiological or biological functions that undergo predictable modifications on exposure to a given dose of radiation. So far this search has not been very successful. Particular attention has been paid to the excretion in the urine of unusual amino-acids or of abnormal amounts of certain amino-acids. For example, the amounts of β-amino-isobutyric acid present in the urine of irradiated patients have been found to be increased, roughly in proportion to the dose. However, many other conditions can cause an increased urinary excretion of this amino-acid and some races normally have a high excretion rate. There are also considerable individual variations. This difficulty might perhaps be overcome by determining normal baselines for persons at risk. Other studies have been concerned with the capacity of the bone marrow to synthesize deoxyribonucleic acid (DNA), and with the mitotic index of the bone marrow, i.e., the fraction of all cells that are in mitosis at any time. Although significant departures from normal occur after irradiation and the changes are undoubtedly dependent on the dose, it has not yet been possible to establish precise correlations.

Recent studies on the effect of radiation on creatine metabolism have given rather promising results. Increased excretion of creatine has been observed in irradiated rats, in patients undergoing radiation therapy, and in victims of radiation accidents. Since creatine phosphate plays an important role in muscle contraction and is normally converted to creatinine before excretion, it is thought that the creatinuria may be due to an inability of the irradiated muscle to utilize creatine and may be related to the muscular weakness often observed in exposed persons. In a study on patients undergoing radiation therapy, some correlation has in fact been found between the degree of creatinuria and the severity of the muscular weakness. In rats exposed to various doses of X-rays, the creatine levels in the urine were proportional to the dose up to 600 r. On the other hand, in accident victims, the creatine levels were not well correlated with the estimated doses. This might mean that the estimated doses were incorrect or that creatinuria is a better indicator of body injury than the dose. It might also be explained by differences in the distribution of the irradiation over the body: there are indications that if the irradiation is directed primarily to muscular parts of the body much more creatine is excreted than if the irradiated regions contain little muscle. Obviously, more studies are needed before it can be decided whether determinations of creatine excretion can be used to assess radiation injury.

For the time being, the principal guide to the severity of radiation injury, apart from the clinical condition of the patient, remains the haematological changes. These are too complex to be discussed in detail here, but usually there is a decrease in all the formed elements in the peripheral blood. Roughly speaking, the higher the dose the more rapid

will be the fall and the lower will be the minimum counts. Obviously, these changes are brought about by damage to the blood-forming organs and they may therefore be misleading if the dose is not uniformly distributed over the body. There are also variations in individual response. Sometimes, paradoxical effects appear, such as an initial rise in the granulocyte count after a heavy exposure. The lymphocyte count is the most generally useful index in the early stages of radiation injury; it nearly always falls precipitately immediately after exposure and the rate and depth of the fall provide some indication of the dose received. However, it is perhaps too sensitive to allow an accurate grading of fairly high doses, since it falls to low levels with doses that are well below the lethal range. At all events, serial blood counts are indispensable in the clinical management of irradiated patients.

Prevention and treatment of radiation injury

Certain chemical compounds have been found to increase the resistance of the tissues to injury by ionizing radiation. Of a large number of compounds that have been tested, the only ones that appear to have a possible clinical application are the mercaptoamine derivatives. The protective action and pharmacological properties of these compounds have been extensively studied, and comparative trials in various laboratory animals have recently been conducted in the USSR. From these it appears that aminoethylisothiuronium (AET) has a better protective action than either cysteamine (β-mercaptoethylamine) or MPA (mercaptopropylamine), and that it is also less toxic. It is not yet known, however, whether AET is sufficiently non-toxic to be administered over a long period to employees engaged in radiation work, nor whether it offers a sufficient degree of protection to justify such administration. The possibility also exists that the administration of AET, or of some other drug, immediately after a known exposure to radiation might reduce the severity of the injury.

In the absence of specific therapy, victims of radiation accidents can be given only symptomatic treatment, but it is important that strict precautions should be taken to avoid complications. In severely injured patients, blood transfusions or other anti-shock measures may be necessary in the early stages. Transfusions of platelet-rich plasma or whole blood have been found beneficial in counteracting any haemorrhagic tendency, particularly in the period 3-6 weeks after exposure. French workers recommend special diets, supplemented by vitamins, amino-acids and liver and adrenocortical extracts. Exceeding all these measures in importance, however, is the prevention of infection. Even relatively low doses of irradiation produce a degree of agranulocytosis that renders the subject peculiarly susceptible to infection. Some workers favour the prophylactic administration of antibiotics, but opinions are sharply divided on the wisdom of this procedure. According to one school of thought, antibiotics should be administered only if an infection occurs and then only after the pathogenic organism has been identified and its susceptibility to the antibiotic determined. Others hold that this procedure involves loss of valuable time and that infection is most likely to be due to one of the common pathogens whose susceptibility to antibiotics is known. While this is undoubtedly true, it is also undeniable that the indiscriminate administration of antibiotics upsets the balance of the normal intestinal flora and may lead to the multiplication of organisms unaffected by the antibiotics, such as the much-feared *Candida albicans*. An intermediate course has therefore been suggested, namely, to take appropriate cultures for identification of the organism as soon as infection is apparent, and then to commence antibiotic therapy while awaiting the laboratory results.

Whether antibiotics are given prophylactically or not, strict asepsis must be practised. Patients are usually kept in isolation in specially disinfected rooms and the number of visitors reduced to an absolute minimum. All visitors wear masks and gowns and observe contagion precautions. Frequent nose and throat cultures are taken and attention is paid to the hygiene of the body orifices. A description of the elaborate sterile

suite that has been installed in the Institut Gustave-Roussy in France will be found in the article on p. 461. While such facilities are of the greatest value in the management of radiation casualties, it has to be remembered that however perfect the asepsis of the surroundings, the patient is still liable to infection from organisms already present in his intestinal tract and must therefore be kept under close observation.

Haemopoietic transplants

With expectant treatment along the lines outlined above, the majority of patients can be tided over the critical phase of radiation disease until spontaneous regeneration of the bone marrow begins and recovery gradually takes place. If the dose of radiation has been very high, however, restoration of haemopoietic function may be very slow and the patient's condition may deteriorate to the point where drastic intervention appears imperative. The discovery that irradiated animals will tolerate homologous grafts [4] suggested the possibility that such patients might benefit from transfusions of bone marrow or of foetal haemopoietic tissue. As already described, this method was tried in the treatment of the victims of the Vinča accident and was apparently beneficial. To be certain that the graft of haemopoietic tissue has taken, however, it is not sufficient merely to observe clinical improvement following the transfusion; it is also necessary to demonstrate proliferation of the donor cells, and this is by no means easy.

To distinguish populations of donor cells from those of the recipient, various types of marker have been employed. One method is to utilize the antigenic characteristics of the blood cells. The red cell or white cell antigens of donor and recipient are determined before the transfusion is made and differences noted. By the use of special agglutination tests it is then possible to follow individually the changes in the two populations of cells. In the case of the Vinča patients, red cell antigens were used as markers, but difficulties were experienced because the patients had been given blood transfusions and the antigenic characteristics of the blood donors were not always known. Nevertheless, on the basis of certain assumptions, it was possible to calculate that the effect of the blood transfusions could not have lasted long enough to account for the observed increase in donor-type red cells. This does not necessarily mean that there had also been proliferation of white cells, although there was some indirect evidence that this had been the case.

One of the disadvantages of using blood cell antigens as markers is that, in order to increase the probability that the graft will take, it is important that the antigenic characteristics of donor and recipient should be as closely matched as possible. In the ideal case, donor and recipient are identical twins: the graft is then described as " isologous " and there are, of course, no antigenic differences by which their blood cells can be distinguished. But even with homologous grafts, the more efficiently donor and recipient have been matched, the less useful are blood cell antigens as markers.

Another method of marking depends on the fact that in the female the granulocytes have a typical nuclear appendage, known as a " drumstick " which is absent in the male. Thus, if a male patient is given a marrow transfusion from a female donor, it is possible to follow the fate of the graft by determining the percentage of granulocytes containing the female drumstick. Not all the female granulocytes have sufficiently well-segmented nuclei for the drumstick to be apparent, however, and in the early stages after transplantation, when many of the granulocytes have a simple lobed nucleus, the number with drumsticks may be very small. Other methods of sex differentiation have therefore been resorted to, such as a detailed chromosomal analysis.

Secondary syndrome

The main function of bone marrow grafts is to keep the patient alive until spontaneous recovery of haemopoietic function takes

[4] Grafts between two animals of the same species but different strains or between human beings who are not identical twins. Normally, such grafts provoke a rapid immunological reaction leading to their rejection.

place. With this recovery, the normal immunological reaction of the host against the graft reappears, and the graft is rejected. This is no disadvantage and may even be desirable. A serious obstacle to bone marrow transfusions is, however, the occurrence of an immunological reaction of the graft against the host. This leads to the production of what has been termed " homologous disease " or the " secondary syndrome ". Although this is a well-defined syndrome in experimental animals, only a few clinical cases have so far been reported. The first signs are fever, nausea, vomiting, diarrhoea and anorexia. These are followed by loss in weight, dermatitis and a greatly increased susceptibility to infections, associated with hypogammaglobulinaemia and lymphopenia. In fatal cases, characteristic histological changes are found at autopsy, such as lymphoid aplasia and necroses of the spleen and liver.

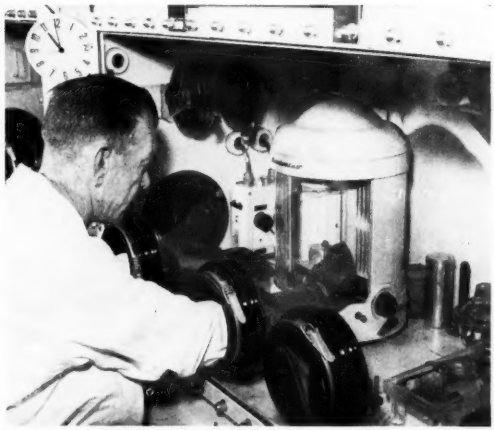
The secondary syndrome is most likely to occur when a very high dose of radiation has made possible a functioning and persistent bone marrow graft in spite of considerable antigenic differences. The bone marrow of the host remains aplastic and there is no host-versus-graft reaction, but the continued proliferation of the transplanted marrow leads to a powerful graft-versus-host reaction. As Loutit has summed it up: " if a permanent graft is induced, one can be fairly sure that the patient would have died early without treatment; but one still has to overcome the secondary syndrome which may be fatal." The problem, therefore, is to obtain a bone marrow graft that will take over the function of the host's marrow until this recovers and will then be rapidly rejected before the secondary syndrome can develop.

The secondary syndrome does not occur, of course, in the case of isologous grafts between identical twins, and it can be minimized by careful antigenic matching of donor and recipient. It has also been suggested that, since the foetus is largely tolerant of foreign antigens, grafts of foetal haemopoietic tissue would be more likely to take and less liable to produce secondary disease. The evidence so far available as to the validity of this argument is somewhat conflicting, though very few studies have yet been made. There are undoubtedly a great many problems involved in the collection, preservation and administration of human foetal tissues. The availability of foetuses for this purpose is influenced by the laws on abortion. The foetuses must be fresh, their sterility assured, and the viability of the cells checked. The liver supplies most of the haemopoietic tissue, but sometimes the spleen is used as well. As a rule, the foetuses used are of 12-28 weeks gestation, but there is much uncertainty regarding the age at which the cells become immunologically active. Nor is it known how the haemopoietic activity of the foetal tissues compares with that of adult marrow. It is therefore difficult to estimate how many cells should be injected; it seems likely that lack of success in the past may have been due to administration of too few cells. One estimate is that a total of 12×10^{10} cells, representing 30 average foetuses, would be needed. The establishment of a large number of foetal-tissue banks would be necessary to make such treatment possible.

It might be added here that secondary disease is not the only hazard associated with transfusions of adult bone marrow or foetal haemopoietic tissue. Micro-emboli have been found in the lungs of animals and patients given such transfusions and this makes it necessary to screen the tissue suspensions very carefully before administration. Shock may also occur, particularly if the injection is made too quickly, and there is evidence that thromboplastin or some other product liberated from the disrupted cells can cause a fatal reaction. The decision to give a haemopoietic transplant to a radiation casualty is thus not one that can be taken lightly. It is not yet possible to say that a patient who has received more than a certain dose of radiation should automatically be given bone marrow—unless, perhaps, it is fairly certain that the dose was in the lethal range. In the present state of knowledge, the wisest course appears to be to watch the clinical developments closely and to give marrow at the first indication that symptomatic treatment is unavailing and the patient's condition steadily deteriorating.

MANAGEMENT OF RADIATION CASUALTIES

Radiation accidents are relatively rare and, to date, only eight giving rise to the acute radiation syndrome have been recorded in the atomic energy industry. Elaborate precautions are taken to protect radiation workers from exposure (1) and in some cases heavy shielding must be provided (2).



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Most of the accidents that have occurred have been due to the presence of unsuspected hazards or to the fortuitous conjunction of several unrelated factors, rather than to carelessness. Thus, in the zero-energy reactor accident at Vinča, Yugoslavia, an experiment was being conducted with the reactor (3) operating at sub-critical levels when a power increase occurred resulting in a critical excursion and exposure of the operators to high levels of gamma and neutron radiation. In the Los Alamos Scientific Laboratory, an accident occurred in 1958 during the recovery of plutonium from liquid wastes: apparently, the material thought to have been " lost " during this process had in fact been retained in one of the tanks and over the years a considerable concentration of plutonium had

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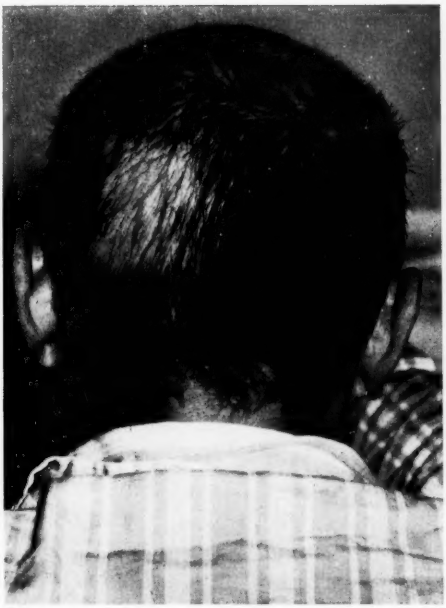
built up; the operation of a mechanical stirring device drew this fissionable material into a critical configuration, with disastrous results. A third type of accident occurred at the Lockport military installation during attempts to tune a new radar transmitter tube without the shield in place (**4**); as no radiofrequency was produced, it was assumed that no radiation was present, when in fact there was an intermittent but intense emission of X-rays.

The signs and symptoms of acute radiation injury in man vary with the type of exposure. Early symptoms following exposure of large areas of the body to high doses usually include headache, weakness, nausea, vomiting and perhaps diarrhoea. Marked erythema and dryness of the skin may be apparent, perhaps associated with conjunctivitis. If the dose to one part of the body has been very large, severe radiation burns may develop; the affected parts become swollen and reddened and enormous blisters appear; surgical debridement reveals a dark-red dermis with small haemorrhagic areas; progressive necrosis may lead ultimately to gangrene.[1] There may be loss of

[1] Colour photographs of severe radiation burns will be found in *Diagnosis and traetment of acute radiation injury*, Geneva, World Health Organization, 1961.



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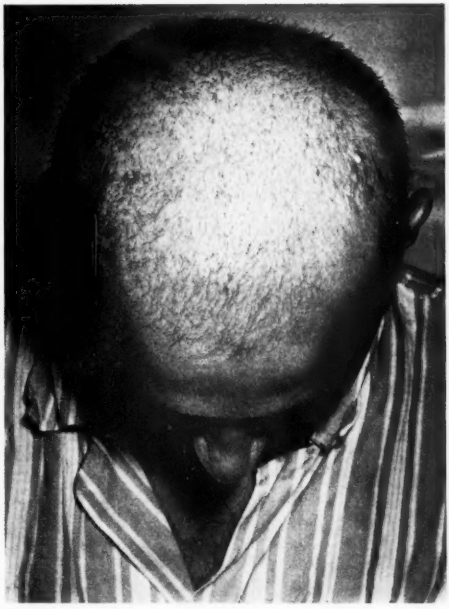

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hair, often asymmetrical (**5**) and sometimes progressing to complete alopecia (**6**). Glossitis and ulceration of the buccal mucosa and gums (**7**) are frequent, and there may be damage to the eye fundus.[2] Striking haematological changes reflect the damage to the blood-forming organs: platelet depression produces a haemorrhagic tendency and the severe agranulocytosis renders the patient peculiarly liable to infection.

Correlation of the clinical findings with the dose received is extremely difficult because of the many factors involved. Exposure is seldom uniform and the same dose can produce very different effects depending upon the part of the body to which it is delivered, and also upon whether it is composed mainly of gamma

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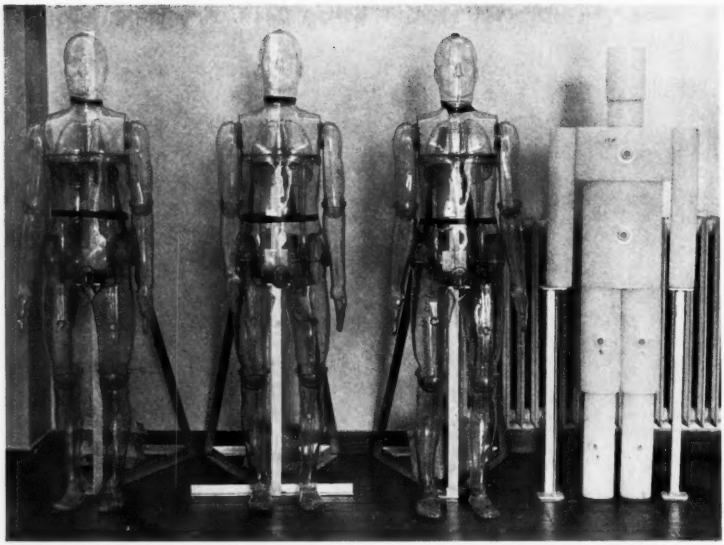
[2] Colour photographs of glossitis, lesions of the buccal mucosa and retinal damage will be found in *Diagnosis and treatment of acute radiation injury*, Geneva, World Health Organization, 1961.



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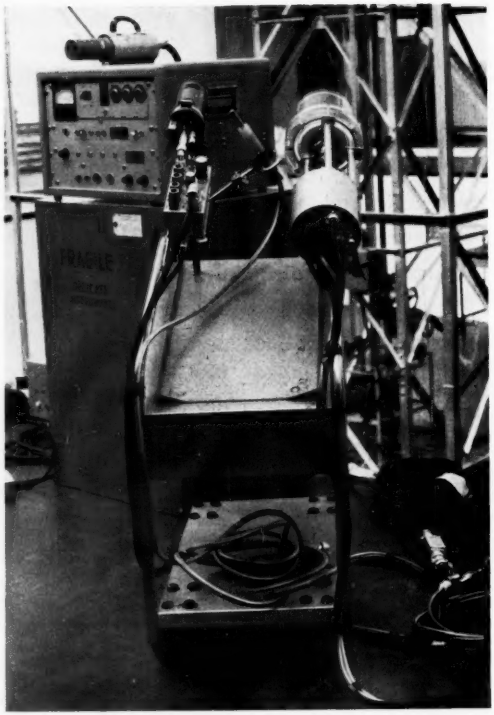
rays, of fast neutrons, or of slow, "thermal" neutrons. By suitable dosimetry studies and careful analysis of all the available data it is usually possible to make rough estimates of the doses delivered to the various parts of the body. The neutron dose can be estimated by determining the amount of the radioactive isotope ^{24}Na formed in the blood from ordinary sodium (^{23}Na) by neutron capture. If the conditions of the accident can be reconstituted, the estimates can be checked by measuring the radioactivity induced in plastic phantoms filled with sodium chloride solution (**8**). By exposing samples of various elements, such as



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gold, uranium, plutonium and neptunium to the neutron radiation and measuring the induced activities, it is possible to determine the energy spectrum of the neutrons. Finally, the gamma-ray/neutron dose ratio can be estimated by measurements with proportional counters and ionization chambers (**9**).

Severe radiation injury occurs after single, acute exposures to more than about 200 r. If the dose exceeds about 600 r, the damage to the heart, gastrointestinal tract, and other organs may be so great that the chances of recovery are slight. Histological examination of the bone marrow shows a great increase in the fat spaces relative to the cellular elements (**10**), when compared with normal marrow (**11**). At autopsy, the brain may show extensive haemorrhage beneath the brain covering (**12**). Many patients who have received doses in the 200-600 r range, however, make a slow recovery if given symptomatic treatment and kept free from complications. Anti-shock therapy may be necessary in the early stages, but the main risks are from haemorrhage and infection, especially during the third, fourth and fifth weeks after exposure.

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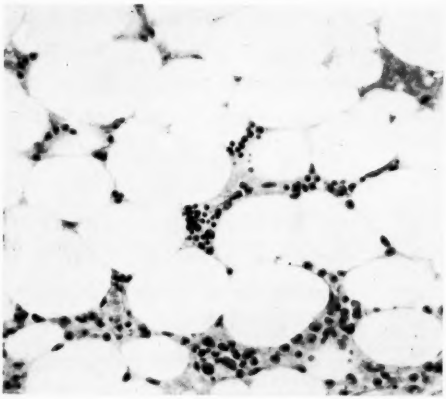

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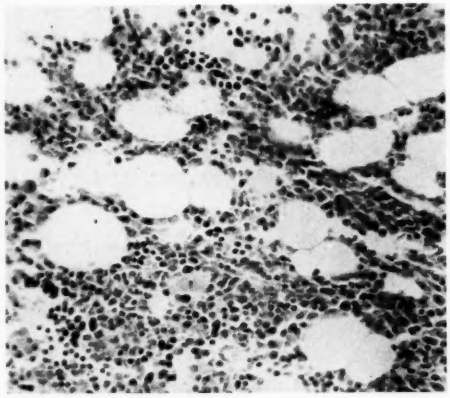

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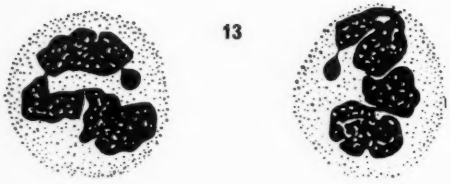
Transfusions of platelet-rich plasma or fresh whole blood have been found of value for counteracting the haemorrhagic tendency, and strict aseptic precautions have to be observed to guard against infection.

Recently, bone marrow grafts have been attempted in severely injured patients to assist recovery of haemopoietic function. Although the results appeared promising, opinion is still divided regarding the value of this form of treatment. In irradiated experimental animals, bone marrow grafts can be obtained with great reliability, but in man the percentage of primary takes obtained so far has been low. To determine whether the graft has taken, it is not sufficient merely to observe the clinical progress of the patient; it is also necessary to demonstrate proliferation of the infused cells. One interesting method of following the fate of the graft depends on the fact that if a male patient is given marrow from a female donor, it is possible to recognize the granulocytes derived from the graft by the presence of " drumstick " appendages on the nuclei (**13, 14**). These appendages are typical of well-segmented granulocytes in the female, but are absent in the male.



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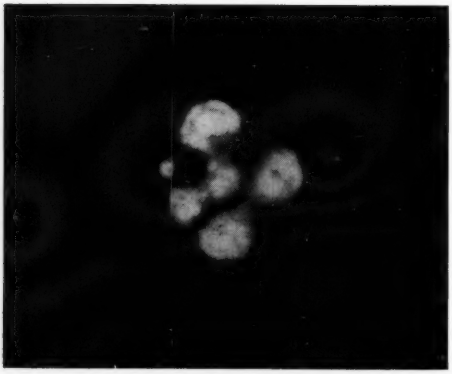

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Irradiation inhibits or destroys the normal immunological reaction of the body to foreign antigens. With recovery of haemopoietic function, immunological activity reappears, however, and even if a successful graft has been obtained, it may be rejected by the host at this stage. There may also be an immunological reaction of the graft against the host. In experimental animals this leads to the production of a very serious complication known as homologous disease or the secondary syndrome. A few clinical cases have also been reported, although it is not a well-defined clinical entity. Nausea, vomiting, diarrhoea, and anorexia reassert themselves, and the patient again becomes

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feverish and a prey to all manner of infections. In spite of recovery in the granulocyte and reticulocyte counts, the blood shows marked lymphopenia and hypogammaglobulinaemia. Skin reactions may occur, such as a rubeoliform eruption changing to exfoliative dermatitis (**15, 16**). If the antigenic differences between donor and

16

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host are large, the secondary syndrome may be rapidly fatal. At autopsy, typical histological changes are found, such as lymphoid aplasia and haemorrhagic zones surrounding necrotic foci in the spleen (**17**).

If some way can eventually be found of achieving a reliable primary take of the administered marrow, the secondary syndrome may become the main stumbling block to the successful use of bone marrow transplants in the treatment of radiation injury. Research is at present being directed to overcoming this complication.

Figures 5, 6, 8, 9, 15, 16 and 17 are reproduced from *Diagnosis and treatment of acute radiation injury*, Geneva, World Health Organization, 1961. Figures 13 and 14 are reproduced from Kosenow, W. (1956) *Triangle*, the Sandoz Journal of Medical Science, **2**, 321, by permission of Sandoz Ltd., Basle. The World Health Organization also acknowledges the valuable help of the following institutions and authors in supplying illustrations for this article: United Kingdom Atomic Energy Authority (1, 2); B. Pendic, Boris Kidrič Institute of Nuclear Studies (3); J. W. Howland, University of Rochester School of Medicine and Dentistry (4); G. Mathé, Hôpital Saint-Louis, Paris (7); Oak Ridge Institute of Nuclear Studies (10, 11 and 12).

THERAPEUTIC USES OF RADIATION INJURY

Much valuable information regarding the effects of large doses of whole-body irradiation and the treatment of acute radiation injury can be obtained from the study of patients deliberately irradiated for therapeutic purposes. Of particular interest in this connexion are the irradiation of patients in preparation for kidney transplantation and the treatment of leukaemia by combined irradiation and bone marrow transfusions. Several stimulating papers on these possible new therapeutic applications of ionizing radiations were read at the joint IAEA/WHO Scientific Meeting on the Diagnosis and Treatment of Acute Radiation Injury (see p. 445). The findings in the patients studied confirm and complement those in accidentally irradiated patients described in the preceding article.

The local application of ionizing radiations has for many years been considered the most effective method of destroying malignant tumours in various parts of the body. More recently, attempts have been made to eradicate malignant blood cells by exposing leukaemic patients to high doses of whole-body irradiation and then administering bone marrow. Although little success has been achieved so far, for reasons discussed later, much has been learned about the effects of ionizing radiations on living cells and tissues, and especially about the responses of heavily irradiated patients to bone marrow therapy. The advantages of studying such patients, as compared with persons accidentally irradiated, are that the conditions of irradiation are accurately known and the dose is uniformly distributed over the body. This applies also to patients exposed to whole-body irradiation in order to lower the immunological defences of the body and thus make possible the transplantation of an organ from a homologous donor—a method recently tried in patients with renal disease. In such cases, no transfusion of haemopoietic tissue is performed, which enables more useful information to be obtained about the blood changes induced by irradiation, particularly as a thorough haematological examination can be made beforehand to exclude any abnormalities in the blood picture.

Kidney transplantation

Until three years ago, it was believed that kidney transplantation was possible only between identical twins. Then came the demonstration that, under certain circumstances, antigenically incompatible tissues can be induced to acquire mutual tolerance. Coupled with the new knowledge regarding the suppression of antibody formation by irradiation, this aroused new hopes. In the USA, a kidney was successfully transplanted to a previously irradiated patient from his non-identical twin. Four further attempts at kidney transplantation in irradiated patients have since been reported from France. In one patient, in whom the indication was chronic renal disease, a kidney transplanted from a non-identical twin was still functioning normally 16 months after the operation and the patient was in excellent general health. Another patient, who had had both kidneys extirpated because of cancer, received a kidney taken from his non-twin sister. The post-operative course was complicated by a series of incidents, but kidney function remained satisfactory until the patient's death, 5 months after operation, from metastases in the liver. A kidney donated by a woman to her sister suffering from chronic renal disease functioned satisfactorily for 3 months. A second irradiation was then performed in

an attempt to prolong the life of the graft, but without success, and the patient died 7 weeks later. In the fourth case, also a woman with chronic renal disease, the donor was a man unrelated to the patient, although there was almost complete identity of the blood-group antigens tested. Renal function remained satisfactory for only 2 months, but in this case a second irradiation brought about a very definite improvement.

These results are, on the whole, encouraging, for there can be no doubt that the grafts persisted much longer than they would have done if the patients had not been previously irradiated. The very long survival of the graft in the case where the donor was a non-identical twin confirms the American experience and indicates a much closer antigenic relationship than normally exists between siblings.

The doses delivered to these patients were 400-450 rad from a cobalt teletherapy unit. Particular care was taken to ensure uniform exposure. To avoid fatiguing the patients irradiation was spread out over about 8 hours; in two instances, this was split up into two sessions, separated by an interval of several days. Naturally, the irradiation not only inhibited antibody formation but also depressed bone marrow function. The doses were so chosen, however, that spontaneous bone marrow regeneration took place without the necessity for bone marrow transfusions. As in all heavily irradiated patients, the clinical course showed four distinct phases: an initial reaction of a few hours' duration, marked by mild digestive disorders; a latent period lasting 2-3 weeks; a critical phase lasting about a week, with rise in temperature, severe agranulocytosis, and deterioration in the general condition; and the period of convalescence. In three of the four patients, wound healing was well advanced by the time they entered the critical phase, but in one case a second operation had had to be performed to relieve congestion of the kidney and scar formation was still incomplete. Healing stopped abruptly, the edges of the wound parted 2-3 cm, and the condition remained stationary for 10 days. But as soon as the temperature fell and the white cell count increased, the wound began to granulate and filled up rapidly. Fever, bone marrow aplasia, and cessation of healing thus appear to be interrelated phenomena.

In the two patients who were submitted to a second irradiation in an attempt to prolong the life of the graft, the reaction was much more violent than was expected. Although the dose was only 100 rad, severe and long-lasting bone marrow aplasia occurred. This finding could not have been predicted from animal experiments, since in animals the response of the haemopoietic system to irradiation returns to normal within a few weeks. In one of these patients the interval was 3 ½ months, but it may be that the hypersensitivity persists much longer. On the other hand, there was no loss of hair nor any changes in serum proteins, such as occurred after the first irradiation.

Of particular interest is the fact that in spite of the high dose of radiation and the severe agranulocytosis, the four patients could be kept free from infection. This was accomplished by isolating each patient in a room containing filtered air, sterilized by ultraviolet irradiation. Entrance to this room was through a second, similarly treated room which communicated in turn with a semi-aseptic storage and changing room where the medical and nursing staff undressed, disinfected their hands and put on sterile clothes and gloves before entering the sterile portion of the suite. Periodic bacteriological examinations were made of samples of air from the sterile rooms and of swabs taken from the attendant staff, and every object taken into the block where the patient was housed was first sterilized. In this way, the concentration of micro-organisms in the air of the patient's room could be reduced to less than 1% of the concentration in the external air.

Study of the patient's microbial flora began before irradiation and included examination of the urine and faeces and of swabs taken from the mouth, other orifices of the body, and the skin. Any pathogenic organisms discovered were eliminated by treatment with the appropriate antibiotic. Routine adminis-

tration of antibiotics was not favoured, however, the greatest importance being attached to preservation of the natural microbial balance. In fact, in some instances where bacteriological analysis had shown deficiencies in the normal flora, aerosols containing the missing bacteria were used to restore the balance. Where a second irradiation was necessary after the patient had been placed in the sterile suite, the cobalt therapy room was sterilized and the patient transported there in a sterile container.

This sterile suite has been set up in the Institut Gustave-Roussy at Villejuif on the outskirts of Paris. At present, very few hospitals have this type of accommodation, but it has been suggested that if the burns units now in existence in certain hospitals were to adopt similar strict aseptic precautions it would not only reduce the risk of infection in badly burned patients but would also enable such units to be used for the treatment of radiation casualties.

Leukaemias

Since haemopoietic function can be destroyed by irradiation and restored by bone marrow transfusions, it seemed reasonable to hope that if all the malignant cells in a leukaemic patient were killed by irradiation and a transfusion of healthy marrow given, only normal cells would be produced by the graft and later by the regenerated marrow of the patient. Unfortunately, the doses of irradiation needed to eradicate a leukaemia appear to be extremely high (about 4000 r). Apart from the likelihood that such doses will cause irreversible damage to the gastrointestinal tract and other organs, there is also the risk of a severe secondary syndrome (see p. 451). Nevertheless, it has been possible to obtain temporary remissions by irradiation and the results are sufficiently encouraging to make it worth while pursuing this line of investigation.

In one series of 20 patients (19 with acute leukaemia and 1 with chronic lymphatic leukaemia) 6 remissions were obtained. These patients had received all the conventional therapy and, with one exception, were in terminal relapse when irradiated. The patient with chronic lymphatic leukaemia had a remission lasting 6 months, terminated by staphylococcal septicaemia. Four of the patients were given bone marrow transfusions from non-leukaemic identical twins after irradiation with doses of 850 r, 1140 r, 1600 r, and 2000 r from a cobalt-60 unit, but all had recurrences of leukaemia within 2-3 months. Other patients received homologous transfusions. It was noted that whereas formed elements began to reappear in the blood after 8-12 days when the bone marrow graft was successful, autogenous regeneration in cases of an unsuccessful graft took about 30 days. It is of interest that a dose of 2000 r (corresponding to 1600 rad) could be given without producing a fatal " gastrointestinal syndrome ". It may be that still higher doses could be used, provided that adequate precautions were taken to avoid complications and that the patient could be kept alive by supportive measures until bone marrow regeneration took place. Much appears to depend upon the dose rate, the orientation of the patient during irradiation, and his distance from the source. The concept of a " lethal dose " of irradiation seems, in fact, to be losing its significance. It must be remembered, too, that developments in the chemoprophylaxis of radiation injury may enable still higher doses to be used in the future.

As mentioned, all except one of the patients in the above study were in terminal relapse when irradiated. Experiments in mice have shown, however, that the effectiveness of irradiation in eradicating leukaemia is in inverse proportion to the number of leukaemic cells present. This suggests that the best results would be obtained by irradiating patients in remission. Furthermore, in mice with a transplanted leukaemia, homologous bone marrow appeared to enhance the antileukaemic effect of irradiation whereas isologous marrow did not (see preceding article, p. 451). There was also a parallel between the antileukaemic effect and the secondary syndrome; those animals that died of a severe secondary syndrome had no evidence of leukaemia, those that died of leukaemia did not develop the secondary

syndrome. The immunological graft-versus-host reaction responsible for the secondary syndrome thus appears to be destructive to the leukaemic cells. Experiments in mice with spontaneous leukaemia seem to confirm this.

It is not certain that these findings can be extrapolated to man but there are indications that they may. Six children suffering from acute lymphoblastic leukaemia were irradiated during remission with doses of 820-950 rad and given homologous bone marrow transfusions. In two cases no graft was obtained and the patients died in a condition of pancytopenia. Of the four patients in whom the graft was successful, two died of a severe secondary syndrome and two had remissions; one survived for a year and the other for 10 months, and in each case they were in complete remission for half the period. What is particularly interesting is that in the two patients who died of a severe secondary syndrome, no histological evidence of leukaemia could be found at autopsy. Both these patients had received marrow from their mothers, whereas in the other cases there was no relationship between donor and recipient. Possibly the mothers had been immunized against the children's antigens during pregnancy, or perhaps the secondary syndrome was more severe because the graft was more permanent.

Obviously, by no means all the possibilities have been exhausted. Apart from increasing the tolerance of the body to high doses of irradiation, it may be possible to reduce the dose needed by combining irradiation with the use of other antimitotic agents. At the same time, ways may be found of preventing or treating the secondary syndrome. One way of avoiding the risk of the secondary syndrome where isologous marrow is not available is by autologous bone marrow therapy, i.e., re-infusion of the patient's own marrow removed before irradiation (or other suppressive therapy) and stored by freezing in a special medium. This has been tried in a number of neoplastic diseases but interpretation of the results was rendered difficult by the absence of markers by which the functioning of the infused marrow could be assessed. The impression was, however, that the infusions speeded up haemopoietic recovery as compared with patients not receiving marrow. Moreover, in irradiated *Macaca mulatta* monkeys, the survival time was increased from a maximum of 16 days to more than 50 days by autologous bone marrow infusions; dogs exposed to " lethal " doses of whole-body irradiation and then treated with autologous marrow have been reported to be in normal health 6 to 20 months after exposure.

It is still much too early to form an opinion as to the ultimate place in medicine of what might be termed " therapeutic radiation injury ". Knowledge of the biological effects of ionizing radiations—particularly of the differing responses of various tissues—is still in its infancy. Perhaps the greatest need is for improved techniques enabling high doses of radiation to be delivered to specific tissues or organs. Such techniques would make it possible to study the effects in isolation and to treat diseased parts of the body without damaging healthy tissues. With a growing insight into the pathological processes underlying neoplastic diseases, it should be possible to utilize the tumour-destroying properties of ionizing radiations more effectively. Perhaps bone marrow therapy will no longer be necessary, or perhaps a better understanding of immunological mechanisms will enable routine use to be made of haemopoietic transplants and permanent grafts to be obtained of many different organs and tissues. But applications may also be found for biological effects of ionizing radiations that have not yet been exploited for therapeutic ends, such as the effects on various metabolic functions. The lethal properties of ionizing radiations are well known; medical research is now proving that these " death rays " can also be " rays of hope ".

VITAL AND HEALTH STATISTICS IN GENETIC AND RADIATION STUDIES

" The techniques for large-scale studies of various aspects of human population genetics are still in their infancy. It is likely that for years to come, each large-scale study undertaken will be encountering field problems and statistical questions not previously solved . . .

" It is difficult to envisage a study on human radiation genetics which would not yield information on a variety of other topics of interest to human biologists . . . Information will also accumulate concerning the total impact of hereditary disease on the populations under study, as well as data concerning mutation rates and other specific items of general genetic interest."

WHO Expert Committee on Radiation [1]

It is now a commonplace that the emphasis in medicine has shifted away from communicable diseases. These diseases, at least in the more temperate parts of the world, appear for the moment to be on the retreat, to be unable to make any headway against the formidable array of drugs and antibiotics opposing them ; and there seems to be no good reason why, with the knowledge and medicaments now available, they should not shortly be on the retreat in tropical countries also. The decline in the importance of communicable diseases has meant that, in addition to chronic conditions, diseases of a different kind have now come to the forefront: on the one hand constitutional or congenital diseases, on the other diseases that are, as it were, a by-product of technological advance, prominent among these being diseases connected in one way or another with radiation.

These diseases differ in many respects from communicable diseases. Whereas in the latter the agent of the disease spreads by contact and the latent period between infection and the onset of the disease is on the whole relatively short, in congenital disease genetic factors are often of paramount importance, and in both genetic and radiation disease the latent period before the disease manifests itself may be years or even decades. As a result, associations of diseases become important; a single gene or a constellation of genes may predispose to several apparently distinct diseases; excessive exposure to radiation may lead to abnormal cell growth, appearing as leukaemia or some other form of malignant disease.

Health statistics, as systems of reporting morbidity and mortality, have been devised primarily with communicable disease in mind. Does the change of emphasis in medicine make any difference to them? This question was discussed at a joint United Nations/WHO Seminar on the Use of Vital and Health Statistics for Genetic and Radiation Studies, held in Geneva from 5 to 9 September 1960.

Genetics and health statistics

From the point of view of a human geneticist—in this case J. V. Neel, one of the participants in the Seminar, in his contribution on " Changing patterns of disease and their implications for vital statistics and genetics "—it is convenient, although an oversimplification, to regard a population as a pool of genes, each generation arising from a sampling of the gene pool of its predecessor. If the sampling, whether random or not, results in a reconstitution of the gene pool, the population is genetically static. If it

[1] *Wld Hlth Org. techn. Rep. Ser.*, 1959, **166**, 23.

results in changes in the relative frequencies of the different genes (particularly if they persist over a series of generations in one direction), the population may be regarded as evolving. Apart from the changes caused by this sampling, the genes do not reproduce themselves accurately generation after generation, i.e., mutations occur, either spontaneously or in response to environmental influences such as radiation.

Most genes are difficult to detect at present because their presence does not give rise to any clearly definable characteristics. Some —such as those producing the blood groups and certain diseases—can be identified in their possessors, and so provide genetic markers for population studies. The frequency of these markers can be determined in populations and comparisons made that will help define similarities and differences between populations and thus degrees of biological relationship. Many of the markers, though collectively important, are individually rare, especially in the field of disease, and systems of disease nomenclature that group diseases of different etiology will not meet the needs of the population geneticist.

The population geneticist wants to know how the genetic situations he encounters have arisen, and what may be expected to happen to them in the future. For this he requires information on the relatives of individuals with certain genetic characteristics, and on the fertility of individuals with specific traits (so as to enable him to determine their contribution to the gene pool of the next generation). These questions have become of increasing importance in a world where the gene pool of mankind is being influenced by radiation, family planning, and the provision of special medical services for children handicapped genetically.

For these purposes, there should be, as well as increased data, increasing utilization of existing data. Additional information is required from birth, death, marriage and other certificates; contributory causes of death are not usually tabulated, but may be of crucial importance to the geneticist; information contained in collections of records ordinarily kept separate needs to be linked. As an example of the difficulties in bringing together all the available information, Neel cited a study his group had recently undertaken into the incidence of congenital aniridia in the State of Michigan, USA. The group had had to consult the records of Ann Arbor University Hospital, the Michigan State School for the Blind, the Department of Social Welfare's Division of Services for the Blind, the same department's Division of Aid to the Blind, the departments of special education of five major Michigan cities (including Detroit), the Records of Vision Section of the Division of Maternal and Child Health, and the Department of Public Instruction's Office of Vocational Rehabilitation; and had in addition to correspond with the records librarians of 165 hospitals and 122 physicians specializing in ophthalmology.

Apart from the additional information that could be elicited from birth and death certificates as they are, more information might possibly be asked for on birth and death certificates: on congenital malformations, for example, or consanguineous marriages. Other possibilities are the linking of records of individuals into family units; special surveys; and the exhaustive cumulative tabulation of data about relatively small geographical and population units of special interest (because of their ethnic background, say, or occupation, or the geology of the region). Neel wondered whether there is not a case for genetic registers on the analogy of the cancer registers already in existence in some countries. There is increasing circumstantial evidence that the frequency of leukaemia may be influenced by even low-level exposure to radiation; a possibility in which the geneticist is interested because of the " somatic mutation hypothesis " advanced to explain the etiology of leukaemia, and the inference that increases in leukaemia rates may bear some constant relationship to increases in germinal mutation rates. If leukaemia were made a reportable disease throughout the world, it would become possible to obtain detailed occupational histories from patients while they were alive. Another source of valuable genetic information is twins. These

are reported on birth certificates, but thereafter they disappear from vital and health statistics and have to be traced by special inquiry.

Statistics and radiation disease

The chief difficulty about assessing the effect of ionizing radiations on the individual —according to R. Doll, another participator in the Seminar, in his paper on " Information sought on somatic effects "—is lack of knowledge about how they induce disease. From animal experiments it is known that certain specific effects can be produced, but the ease with which they can be produced varies so greatly that no generalization is possible; nor are experiments readily possible in man. Two questions need an answer. One is: what is the range of effects that may be produced by radiation? A fairly clear idea of the acute effects exists. The delayed effects are known to include many, if not all, types of cancer; local effects on individual tissues, such as cataract and sterility; and a reduction in the expectation of life. Irradiation of the foetus is known to produce abortion, stillbirth, and microcephaly. What is not known is whether the reduction in the expectation of life is due to a non-specific acceleration of all the processes of aging or whether the average reduction observed in a group is the sum of various specific effects occurring in individuals. While the principal specific effects are probably known, it cannot yet be said that no other effects can be produced or that all the possible effects in the foetus are known.

The second question that needs an answer is: what is the relationship between the various parameters of radiation dose and the incidence of the effect? This is a more complex question, because the relationship is likely to vary with the physical conditions in which the dose is given, and both dose and incidence have to be measured accurately.

From what sources can information be derived, and what can vital and health statistics do to help answer these questions? The sources of information are listed in the following table.

POPULATIONS EXPOSED TO DIFFERENT AMOUNTS AND DIFFERENT TYPES OF RADIATION

Type of exposure	*Specific populations*
Normal background	Residents at low and high altitudes Residents in areas of different geological structure, e.g., on thorium sands, in towns built of granite, in areas with high and low radium content in water supply, etc.
Artificial changes in background	Persons exposed at different periods of development to variations in background due to fall-out from test explosions or atomic energy accidents
Occupational exposure	Uranium miners Luminizers Radiologists Medical and industrial radiographers Atomic energy workers (normally and accidentally exposed)
Medical exposure	Patients examined radiographically or by means of radioactive isotopes Patients treated by radiotherapy Foetuses exposed in utero
Atomic bomb explosions	Survivors at Hiroshima and Nagasaki

From these, data may be obtained that will allow a comparison of the effects of different levels of dose. One example is the proposed follow up of patients treated by radiotherapy for cancer of the cervix. The dose given will be measured and the patient kept under direct observation to discover the incidence of leukaemia. A difficulty about

this sort of study is that a long time may elapse before the results are obtained; another is that, if the dose of radiation is small or the incidence of the effect low, the number of subjects required is large. A simpler method is to organize an automatic follow up of a defined population. Here success depends on the adequacy of (1) the diagnosis in the general population and (2) the routine description of the dose. Time can be saved by defining a population that has already been treated and following the subjects from a date in the past up to the present. Retrospective "case history" inquiries, which begin from an affected individual, can also be useful. In fact, it is doubtful whether there is any other practical method of assessing the effect of very small doses.

Vital and health statistics can help in these inquiries by identifying individuals in the population and enabling them to be followed up. They are particularly useful for this purpose in Japan, where all the individual's legal records—his birth, marriage, and death certificates—are kept together in the municipal area where he is deemed to reside. One simple improvement that would facilitate identification and follow up would be to record the date and place of birth on the death certificate, as is done in New Zealand, the USA, and elsewhere. These combined records have been used in the USA to study the effects of intra-uterine irradiation; they could be used as a partial check on the residential history of persons who die in areas with different amounts of background radiation. International agreement to record the causes of stillbirth would also be useful. Another improvement would be the definition of a group of conditions that could serve as an index of the incidence of congenital malformations—for at present observers disagree not only about what they regard as a significant abnormality but also about the extent to which diagnosis should be pursued (e.g., whether abnormalities should be included that are discovered only on autopsy). Efforts to improve medical certification and classification of the cause of death should be intensified, particularly when death is due to either of the two causes—leukaemia and bone sarcoma—that have been most used in recent years to indicate long-term radiation effects in the individual. Leukaemia is clearly not a single disease; the etiology of the various forms is likely to be distinct; and each type should be recorded separately. Doll had conducted a survey into mortality from bone tumours in England and Wales and had found that after the age of 24 years the proportion of deaths attributed to bone tumours in which the diagnosis had been correctly classified fell off rapidly. The fault lay, however, less with the certifying doctors than with the international rules; these result in the attribution of many secondary cancers or carcinomas of epithelium covering bone to primary tumours of bone, whereas this was clearly not the intention of the certifying doctors.

Some of these points were touched upon by other participants in the Seminar. H. L. Dunn, of the US National Office of Vital Statistics, thought that a committee should re-examine the categories of the International Classification of Diseases in so far as they relate to genetic disease. The poor quality of medical diagnosis of such disease is a difficult problem with which to cope. Perhaps, in view of the medical profession's great interest in radiation and the mutation rate, it could be persuaded to take more care with diagnosis. Dunn looked with some misgiving upon any suggested addition to death or birth certificates. "The good will and time of thousands of physicians are involved with filling out these documents. A single additional item calls forth much grumbling among those who record the answers, and several new items put on just 'for statistical purposes' would be likely to cause a rebellion." In his opinion, the brightest promise of securing the additional information needed in human genetics lies perhaps in studies linked with vital records, such as were started some years ago by the US National Office of Vital Statistics. Since birth and death certificates could not be expanded to any great extent, this office held that special studies should be carried out to collect the additional information required; and so far the medical profession has co-operated with enthusiasm.

Genetic information by electronic computer

The use of the electronic computer to derive genetic information from routine vital statistical records was discussed by H. B. Newcombe & P. O. W. Rhynas, and by J. M. Kennedy, of the Atomic Energy of Canada Limited. Other data-processing equipment for record linkage was described by S. Binder of National Analysts Inc., Philadelphia. The basic step—said Newcombe & Rhynas in their paper "Family linkage of population records"—consists of "linking" birth registration with the parents' marriage registrations in order to establish family groupings. Once this has been done, records of deaths and of ill health can be linked to the family groups and pedigrees traced; if needed, other records providing social and economic information could theoretically be integrated into the system, and the pedigrees lengthened by the introduction of later generations of marriage and birth records. As the linking of records is governed by rules that can be set down in advance, a programme can be written down for execution by a general-purpose computing machine.

This has been done with birth and marriage records in British Columbia. A file of some 114 000 marriage records has been set up, covering the ten-year period 1946-1955, and is being linked with birth records for the period 1946-1958 (about 400 000 records), records of deaths for the period 1946-1959, and records of stillbirths, congenital abnormalities, and handicapped children, for analysis by the computer. The two surnames on each record are coded phonetically and the final files set up on magnetic tape. With this programme the machine can examine about 1500 births and produce 800 linkages between births and marriage per hour. Although the use of the computer to obtain this kind of information is still in its infancy, Newcombe & Rhynas calculate that, as compared with manual procedures, failures to bring together potentially linkable records will be reduced from 17 to 2 per thousand, while false linkages will be reduced from 2 per thousand to less than a tenth this frequency.

The results so far are limited to those derived from the linkage of two years of births to ten of marriages, and are more valuable for what they promise than for what they have achieved. The kind of study that would be much simplified by this method would be the follow up of the consequences of clinical irradiation. For example, if the project were extended to include punch-cards for all hospital records of pelvimetries in British Columbia related to the 13 years of births included in the present plan (estimated at 26 000 pelvimetries), and a further ten years of deaths were added to detect all deaths from leukaemia and other malignant conditions up to the age of 10, the size of the project would be increased by about 20%. In the United Kingdom the malignancy rate following pelvimetry has been shown to have doubled.[2] There the method used was the much more laborious one of personal interview; with the computer, not only would there be many more data, but they would be less subject to error and to faulty individual memory.

Radiation dose and effect

The Seminar discussed present sources of information, on the basis of papers reviewing methods, procedures and limitations of vital and population registration as now practised, certification and recording of causes of mortality, and recording of morbidity. Then it turned to the assessment and recording of human radiation exposure. It is undeniable —maintained B. Lindell, of the Institute of Radiophysics, Stockholm—that even one quantum of radiation could kill a cell, and this obviously frequently occurs. But there is no evidence whatsoever that any mutational effect or other injury at the level of the cell will develop into a malignant growth that will manifest itself at a later stage unless the number of primary effects is sufficiently high and their distribution over time sufficiently narrow. In other words, there is no conclusive evidence that a threshold radiation dose does not exist. Nevertheless, a non-threshold,

[2] Stewart, A., Webb, J., & Hewitt, D. (1958) *Brit. med. J.*, 1, 1495.

linear dose-effect relation has often been assumed, with little hope of the assumption ever being proved correct because of the very high number of individuals who would have to be studied to prove it. Even negative information can be of value, however, Lindell held, and he proceeded to show this statistically. On the assumption of a linear, non-threshold dose-effect relationship, the average dose is the valuable parameter, and it may be averaged over the relevant body tissues and over the population. Any epidemiological correlation will be made on a statistical basis, and the individual doses need not be known, it being sufficient to know the average dose in the population. The necessary data may be derived from pilot studies and from available statistics on age distribution, dose ranges, etc. The drawback to the statistical method of proving a non-threshold, linear dose-effect relation is that large populations would have to be studied. Most data about exposure of large populations are derived from the whole population of a country, and estimates of weighted averages for genetic dose and bone marrow dose have been made for some countries. If a whole population is studied, the control population would have to be the population of a neighbouring country. If on the other hand correlation studies seek to prove a non-linear dose-effect relation, the populations available must be split into groups with a similar exposure, or sufficient information must be obtained to make an individual correlation between disease and exposure possible. Whatever the aim, the difficulties are great.

The survivors of Hiroshima and Nagasaki

Another paper contributed to the Seminar, by J. W. Hollingsworth and co-workers, described the work of the Atomic Bomb Casualty Commission on survivors in Hiroshima and Nagasaki. Theoretically, and indeed practically, more information could be, and has been, obtained from this work than from any other source; but there have been many difficulties. It has been difficult, for example, to determine the radiation dose received, and to find acceptable controls. What vital and health records, in the light of the Commission's experience, could help forward research into the somatic effects of radiation? Certain general procedures would be valuable: the registration of persons with significant exposure, the linkage of death records with birth or other routine vital records, and the registration of tumours. Registration would provide samples for study. With the sample, the investigator needs to look for significant, unbiased follow-up information, and the linkage would provide this. So would a tumour registry.

This paper outlined briefly what had been discovered as a result of the Commission's work. In a sample of 6000 births where one or more of the parents had been exposed within 2000 metres of the bomb hypocentres, it was found that the incidence of major congenital abnormalities, stillbirths, and neonatal deaths was not significantly different from that in the non-exposed population. Genetic damage has been found not to be a marked late effect of a single radiation dose of moderate degree; the findings define a certain upper limit of potential genetic damage in human beings, but the population at risk is too small to estimate genetic damage response to a single exposure dose. Late radiation effects on growth and development have proved difficult to assess in survivors of the Hiroshima and Nagasaki bombings, because of inextricable mingling of radiation effects and the economic, social and medical effects of the disruption of families and public health facilities; really suitable controls have also been hard to find. Nevertheless, what evidence is available indicates delayed maturation in children exposed to the bombing, but the specificity of the finding as a late radiation effect is open to doubt. The appearance of microcephaly makes it fairly probable that a large dose of radiation received by the foetus in the early months of gestation inflicts serious damage on the developing brain. Other late effects are radiation cataract and leukaemia. There has been a considerable increase in the incidence of leukaemia in irradiated groups; the rate in the whole of Japan is 20-30 cases per million population per year, and this is the observed incidence

in the non-irradiated populations of Hiroshima and Nagasaki. In the radiated populations, on the other hand, the incidence rose to just under 300 per million per year 6-7 years after the bombing, all kinds of leukaemia being concerned except chronic lymphatic leukaemia. The incidence decreased the farther those exposed had been from the hypocentre. The evidence appears to favour the hypothesis that the dose-response relation is linear, but is insufficient to settle the question whether there is a threshold for irradiation that will produce leukaemia.

A tumour registration system was set up in Hiroshima and Nagasaki, and it would appear from analysis of the cases entered that carcinoma develops only after many years of latency following irradiation. Along with mortality and clinical studies, analysis of the tumour registers should in a few years confirm this finding and perhaps allow a reasonable estimation of the dose response in man for radiation-induced carcinogenesis. The evidence about the effects of radiation on fertility is as yet incomplete. It has been known for a long time that therapeutic irradiation has permanent effects on both ovarian and testicular function, but little has been discovered about the effects of the bombing except that menstruation stopped in a number of cases well above normal expectations. But most of the women concerned were nearing the menopause or had pre-existing disease of the ovaries. Finally, so far there has been no evidence to show that the processes of aging are accelerated by irradiation.

Other subjects discussed

J. T. Boyd, of the Medical Research Council Statistical Research Unit, London, described the preliminary findings of a follow-up study from available records of workers in the British luminizing industry. It proved both possible and practicable to trace these workers and submit them to tests to assess their radium burdens.

Several participants described methods of using routinely collected information for genetic purposes. A. Moroni, of the Genetics Laboratory, University of Parma, had used, for the study of consanguinity, records of baptisms, marriages, deaths and population censuses (*status animarum*) kept by Roman Catholic priests in every parish in Italy since the Middle Ages, and in some cases by the bishop or in Rome. Toshiyuki Yanase, of Kyushu University, Japan, described the unique registration system that has arisen in Japan from the traditional family structure. The family register is compiled with the head of the family as the central figure. The location of the family is described as the permanent domicile, although the family may no longer reside there, and every member is entered in the register, along with all changes in his or her personal status—adoption, divorce, death, etc. The result is that, despite certain limitations, these registers provide unrivalled information about consanguineous marriages and matrimonial migration. Their value was shown in a paper by W. J. Schull & J. V. Neel, of the Department of Human Genetics, University of Michigan, USA, on a genetic survey in Japan of 4598 children born of related parents in Hiroshima and Nagasaki between mid-1948 and the end of 1953. The whereabouts of each child could be determined once the family's permanent address (*honseki*) was known.

Other participants described national health surveys as a source of morbidity data for genetic and radiation studies, and various methods of using demographic data. A.G. Stevenson, of the Medical Research Council Population Genetics Research Unit, Oxford, England, stressed, however, that no amount of routine collection of information, whether by central government bodies, local government bodies, hospitals, clinics or voluntary agencies, will ever result in data that do more than provide fragmentary, even if essential, information. Where vital and health statistics are useful is in furnishing a starting-point for investigations (otherwise the population will have to be screened *de novo*), in giving a broad picture of orders of magnitude, frequency, and associations of the phenomena to be surveyed, in providing a check on whether cases discovered by other

methods are representative of the population, and in furnishing comparisons of viability and fertility of affected individuals and of parental age and parity effects.

* * *

The Seminar as a whole was convinced that an era is beginning in which knowledge of the genetic endowments of human beings and of populations will lead to new insights into the health and well-being of mankind. It felt that contacts between biological scientists and vital and health statisticians should be maintained and expanded and that civil registration authorities and biologists should consult frequently on matters of common interest. The duties of civil registration authorities are to a considerable extent legal and administrative, and procedures for the collection of vital statistical information are not, and cannot be, designed to meet the needs of human biologists only. Nevertheless, any progress in the human biological sciences can have wide repercussions in other disciplines, like demography, of recognized significance for the economic and social welfare of the community.

The Seminar felt that any alteration of existing procedures should be assessed in the light of the local situation. Alterations can often be achieved fairly simply, without drastic changes in the existing systems. The following examples of desirable change were singled out.

(*a*) Information available from routine records could be supplemented by linkage with other records relating to the same individual.

(*b*) Segments of biological families could be reconstructed through record linkage so as to permit longitudinal studies over a number of generations.

(*c*) Information could be recorded so as to identify consanguineous families and thus make it possible to assess the effects of consanguinity on the survival, health, and growth of offspring.

(*d*) Partial or complete registers could be set up of population groups of genetic and medical interest, such as twins and people suffering from hereditary diseases, congenital malformations, and malignant diseases.

(*e*) Additional entries requesting information sought for analysis or linkage and special tabulations could be introduced into vital and health statistics.

(*f*) Data for the assessment of frequency patterns and differentials could be better and more extensively used.

(*g*) The estimation of doses given to patients during X-ray work could be made easier, for example by keeping records of normal practices, types of equipment, etc. in X-ray departments.

(*h*) The quality of the basic data could be improved, by the removal of ambiguities in terminology and in the structure of questions, the querying of imprecise replies, and the inculcation of an increasing awareness of their responsibilities in certifying physicians and other informants.

(*i*) A list of pathological conditions of genetic significance could be developed that would usefully supplement the International Classification of Diseases.

(*j*) Attempts could be made to make records easier of access for research.

The Seminar concluded that: " The present state of development of human biology requires flexibility of approach, and the contribution of vital and health statistics to genetic and radiation studies will have to be judged on results which may not emerge immediately. Some of the possible approaches will prove more fruitful than others, but increasing knowledge in these fields is bound to be of the greatest social benefit."

Notes and News

The doctor in the community

The importance of comprehensive medical care, which stresses prevention as well as diagnosis and treatment, has been repeatedly emphasized by WHO expert groups on various aspects of medical education. During technical discussions on "Public health as a scientific discipline" at the tenth session of the WHO Regional Committee for Europe in 1960, it was suggested that WHO should convene a meeting to discuss medical curricula from this point of view. Following up this suggestion, the WHO Regional Office for Europe held a Conference on the Training of the Doctor for his Work in the Community, from 21 to 29 September 1961, in Edinburgh. The Conference brought together representatives of different branches of medicine interested in medical education as a whole, irrespective of their particular specialties. The participants came from more than 20 countries in the European Region.

In Europe, growing medical specialization appears to have produced a decline in the number of doctors without specialist qualifications or interests. One purpose of the Conference was, therefore, to ascertain whether specialists alone can give the public all that medicine can and should offer, or whether a branch of the profession responsible for general medical care and for the maintenance of community health is not still necessary.

Another, even more important, purpose was to take stock of possible deficiencies in the education and training of the doctors mainly responsible for medical work outside hospitals, and review ways and means of remedying them.

While recognizing that the preparation of a doctor is inevitably a long and continuing process, the Conference concentrated on those improvements in both education and training it considered to be most appropriate to the undergraduate period. In particular, it discussed ways not only of providing students with knowledge and clinical experience, but also of developing their ability to use their knowledge for the solution of clinical problems.

O'nyong-nyong fever and malaria

In a central district of Uganda during 1960 a considerable fall in malaria rates and transmission was found to be associated with the occurrence in the area of o'nyong-nyong fever, a new epidemic virus disease of East Africa. This disease, which clinically closely resembles dengue, was first noted in 1959 in north-western Uganda[1] and spread south and east into Kenya to reach Lake Victoria, causing some 750 000 infections with no deaths. It is characterized by fever, headache, rash, and severe pains in the joints and back (the name o'nyong-nyong means "joint-breaker"). Evidence obtained by the East African Virus Research Institute indicated that the virus is harboured by the two main African malaria vectors, *Anopheles gambiae* and *A. funestus*, and is certainly transmitted by the latter.

The recent observations[2] reported by WHO staff members and others from the Uganda Malaria Eradication Project and from the East African Virus Research Institute refer to malaria investigations centred on the town of Rakai, where conditions vary between hyperendemic and mesoendemic. During the month of May 1960 it was found, unexpectedly, that despite meteorological conditions and high vector densities favouring malaria transmission the sporozoite rate was remarkably low. Out of 533 *A. gambiae* dissected in that month only 3 had sporozoites in their salivary glands and none were found in 295 specimens of *A. funestus*. This unexpectedly low sporozoite rate was accompanied by a sudden drop in malaria rates in the local school-

[1] Haddow, A. J. et al., *Trans. roy. Soc. trop. Med. Hyg.*, 1960, 54, 517.

[2] To be published in the *Bulletin of the World Health Organization*.

children (the parasite rate was 10.7% compared with 52.6% in December 1959) and by the appearance of o'nyong-nyong fever in the area. The virus was isolated from both patients and mosquitos and the virological findings indicated a peak of mosquito infections in May, followed by a high number of human cases in June and a waning of the epidemic in July.

Thus a great reduction of malaria transmission occurred at the very time when transmission would normally have increased, and when the vector species were transmitting o'nyong-nyong virus very efficiently in the area. This suggests the possibility that the virus may have inhibited the development of the malaria parasite in the mosquito or the human host; or, alternatively, that it may have modified transmission by shortening the life of the vector. Some interaction is known to exist between viruses and avian malaria parasites,[3, 4] and the same may be true of the o'nyong-nyong virus and human malaria, although final proof must await experimental work on monkeys, human volunteers or malaria-therapy cases.

Hypertension and ischaemic heart disease

Vital statistics suggest that hypertensive disease and ischaemic heart disease together account for a high proportion of all deaths, even at relatively early ages. Thus, in 1958, these diseases were responsible for 15% of all deaths between the ages of 35 and 39, and 40% of all deaths between the ages of 50 and 54 in Australia, Austria, Canada, Denmark, Finland, Germany (Federal Republic, West Berlin), Hong Kong, Hungary, Ireland, Israel, Italy, Japan, the Netherlands, New Zealand, Norway, Portugal, Sweden, Switzerland, Taiwan, the United Kingdom, the USA, and Yugoslavia.

Hypertensive disease seems to be an important cause of death in many parts of the world. Mortality from ischaemic heart disease is particularly high in the developed countries, and may be expected to increase in those undergoing rapid development, unless adequate measures are taken.

At present the etiology of these diseases is unknown, although there are several hypotheses, some strongly supported by observation, but none that can be regarded as proven. It appears, however, that certain known health and medical care methods may prevent them or change their usual course, though these measures cannot be recommended to public health authorities without intensive world-wide investigation of their effectiveness.

WHO has therefore asked 74 scientists from 37 countries to define the stages of hypertensive disease or ischaemic heart disease at which measures could be taken which would prevent deterioration, to define these measures, and to indicate what types of research can most usefully be undertaken on these diseases.

The replies so far received (from 49 scientists) have been analysed and provided a basis for discussion at the meeting of a WHO Expert Committee on Public Health Measures in the Prevention and Control of Arterial Hypertension and Ischaemic Heart Disease, held in Geneva from 16 to 23 October 1961. It appears that, while opinion on certain details varies considerably, there is a wide measure of agreement on the basic features of the " stages " of the two diseases. The suggestions received on the large-scale use of certain existing therapeutic measures and on research were considered by the Committee, which made practical recommendations on the basis of the available evidence.

An account of the Expert Committee's work will appear in the *WHO Chronicle* at such time as its report is published.

Irradiated foods

The wholesomeness—including the nutritional adequacy and harmlessness—of irradiated foods was the subject of a technical meeting held jointly by FAO, IAEA, and WHO in Brussels, from 23 to 30 October 1961. The purpose of the meeting was to review the most recent work on the subject and to make recommendations that might provide a technical basis for legislation on the production and use of such foods. Methods of testing the wholesomeness of irradiated foods were discussed in relation to the more general problem of food additives.

[3] Barnett, H. C., *Amer. J. trop. Med. Hyg.*, 1956, **5**, 99.
[4] Trager, W., *Proc. Soc. exp. Biol.*, 1959, **101**, 579.

The findings and recommendations of this meeting will be reviewed in full in the *WHO Chronicle* at such time as they are published as a joint report.

Nursing administration in South-East Asia

A Regional Conference on Nursing Administration will be held in Kandy, Ceylon, from 23 November to 3 December 1961, under the auspices of the WHO Regional Office for South-East Asia. Nursing leaders from all countries in the Region have been invited, and the two Regional Nursing Advisers will be present. The International Council of Nurses and the US International Cooperation Administration have also been asked to send representatives.

The subjects to be studied by the Conference include: general administration and the application of its principles to nursing education, human aspects of management, the development of nursing as a profession, preparation for administration in nursing, the importance of professional organizations nationally and internationally, the organi ation and co-ordination of nursing services to meet changing needs, and the aims and objectives of nursing service administration.

Course on radiation health

An international training course on radiation health and safety was held jointly by IAEA and WHO, in co-operation with the Government of Japan, at the National Institute of Radiological Sciences, Chiba City, Japan, from 24 October to 21 November 1961. There were some 20 participants from countries in the Western Pacific and South-East Asia Regions.

The course dealt broadly with the basic principles, both physical and biological, involved in radiation health, and with the main problems arising in practice, including those associated with the medical and industrial use of X-rays, radioisotopes, and other radiation sources, with the public health aspects of atomic energy activities and radioactive waste disposal, and with radiation protection in atomic energy operations.

Inter-Regional Leprosy Training Course

WHO is holding an Inter-Regional Postgraduate Leprosy Training Course for doctors from the African, Eastern Mediterranean, South-East Asia and Western Pacific Regions, in Manila, Philippines, from 20 November to 9 December 1961.

The Government of the Philippines has provided facilities for holding the course in Manila and Cebu, and Dr J. N. Rodríguez, Director, Bureau of Disease Control, Department of Health, has been appointed Technical Director of the course.

Most of the participants are, or will be, in charge of the leprosy control services in their respective countries, and the programme for the course stresses the preventive aspects of leprosy control, as well as individual treatment. Special emphasis will be laid on practical training and, in addition to lectures, there will be clinical seminars, laboratory work, study of leprosy campaign files, and field trips.

Nutrition in Asia

The Joint FAO/WHO Nutrition Committee for South and East Asia will meet in Hyderabad, India, from 1 to 8 December 1961. Participants have been invited from all Member States in the South-East Asia and Western Pacific Regions of WHO, and from Pakistan. Representatives are expected from ILO, UNESCO and UNICEF, and from such organizations as the South Pacific Commission and the League of Red Cross Societies.

The subjects to be discussed include: progress in the nutrition work of FAO and WHO in South and East Asia, the organization of education and training in nutrition, nutrition in pregnancy and lactation, nutrition problems of pre-school children (hypo-vitaminosis A, protein malnutrition) and their prevention, and anaemias.

The Joint Committee will meet at the National Nutrition Research Laboratories of the Indian Council of Medical Research, which were recently moved to Hyderabad. Participants will thus be able to study at first hand the work of these laboratories in basic research, applied nutrition, and education and training.

People and Places

Water supplies in Pakistan

A WHO team of consultants on domestic water supply is spending two months (October and November 1961) in Pakistan to help with the engineering, organizational and financial aspects of a community water supply programme for the province of West Pakistan.

The leader of the team is Mr Clarence Klassen, of the United States, who is dealing with organizational and administrative aspects of the programme. Mr T. B. Nicol, of Australia, is concerned with engineering and operational aspects, while Mr K. M. Hepburn, of the United Kingdom, is advising on finance and general administration.

As Chief Sanitary Engineer for the Illinois State Health Department, Mr Klassen has many years' experience of the administrative aspects of water supplies, sewerage systems, and the development of water resources for community purposes. Of particular interest is his work in connexion with the interstate control of water development and water pollution in the Upper Mississippi and Ohio river basins. Mr Klassen has served as WHO consultant in sanitary engineering projects in Japan, North Borneo, and China (Taiwan), and at a WHO seminar on community water supplies held in Amalfi, Italy, in 1960. He has also advised the WHO Regional Office for Europe on the administrative aspects of water pollution control.

Mr Nicol recently retired after some forty years' service as Engineer-in-Chief, Metropolitan Water, Sewerage, and Drainage Board, Sydney, Australia. This is his first international assignment.

Mr Hepburn is at present Director and General Manager, East Surrey Water Company, where he has held responsible posts for some thirty years. He is a Fellow of the British Institute of Chartered Accountants, and is an internationally recognized expert on the administration and financing of water supply systems.

Control of filariasis

Dr G. Burnett, Deputy Director and Head of the Medical Entomology Section, Tropical Pesticides Research Institute, Arusha, Tanganyika, has been appointed WHO consultant on the planning of research into the biology, ecology and control of mosquito vectors of filariasis (in particular *Culex fatigans*) under the WHO expanded programme of medical research. As a first step, Dr Burnett will carry out a survey of the effectiveness of mosquito control methods at present used in India, Ceylon, Malaya and Burma. This survey will be similar to that on *Simulium* control carried out by Dr A. W. A. Brown in Africa in 1960.

Improving nutrition in Kenya

WHO and FAO are giving technical assistance and UNICEF financial aid to a nutrition programme planned by the Government of Kenya. The programme aims at improving the nutritional situation of the population of Kenya through education, supplementary feeding, and the rational organization of food production.

Miss Anne Burroughs has been appointed non-medical nutritionist to this programme, and will be responsible for planning and conducting preliminary dietetic surveys, which—with clinical surveys—will be used to ascertain the nutritional situation.

Miss Burroughs is a graduate of the University of Vermont, and has had postgraduate training at the Harvard School of Public Health.

Development of rural health

Dr Carlos Luis González, Technical Adviser to the Ministry of Health of Venezuela, has accepted a three-month appointment with WHO to study ways in which pre-eradication malaria programmes may be combined with the development of rural health services. In the course of this assignment, he will visit Ethiopia, Morocco, Togo, Dahomey and Nepal, and the WHO

Regional Offices at Alexandria, Brazzaville and New Delhi.

Dr González received his basic medical education in Venezuela and his Doctorate in Public Health at the Johns Hopkins School of Public Health, Baltimore, Md., USA. He was appointed to the Health Service of the Government of Venezuela in 1939, becoming Director of Public Health in 1949, and later serving for a time as Minister of Health. For five years he was Assistant Director of the Pan American Sanitary Bureau, which acts as WHO Regional Office for the Americas.

Malaria eradication in Burma

Dr Fernando Machado de Bustamante has been appointed short-term WHO consultant to assess the needs of the malaria eradication programme in Burma and to help the Government of Burma develop a comprehensive plan of operations for the completion of the programme.

Dr Machado de Bustamante, who was until recently Director of the National Malaria Eradication Service of Brazil, has specialized in malariology for over twenty years. He received his medical education at the University of Rio de Janeiro and, after taking a malariology course in Brazil, joined the Rockefeller Foundation's North-East Malaria Service which was responsible for the elimination of *Anopheles gambiae* from Brazil. Dr Machado de Bustamante subsequently studied malariology in Venezuela and the USA, and in 1955 he was awarded a WHO fellowship to visit Mexico, Panama, Venezuela and British Guiana. He has served for a number of years on the WHO Expert Advisory Panel on Malaria and the Advisory Committee on Malaria Eradication of the Pan American Health Organization.

Sanitarian for Cambodia

Mr Bishara Shehadeh has been appointed WHO sanitarian at the Rural Health Training Centre, Takhmau, Cambodia, where a team of international experts is helping the Government of Cambodia build up public health services and give field training to public health workers. The training centre is helped by UNICEF and WHO under the United Nations Expanded Programme of Technical Assistance.

Mr Shehadeh, who holds a certificate in sanitation from the American University of Beirut, served as teaching assistant at the University from 1954 to 1957 after two years as District Sanitarian of the United States Operation Mission (USOM) in the Lebanon. Until November 1960, he was a staff sanitarian with the Libyan-American Joint Public Health Services in Libya.

Exchange of teaching staff

Dr Alexander G. Gilliam, Associate Professor of Epidemiology at John Hopkins University School of Hygiene and Public Health, Baltimore, Md., USA, has recently been appointed WHO consultant in epidemiology to the Institute of Hygiene, University of the Philippines. He will help the Institute organize and conduct courses in epidemiology for graduate and undergraduate students and develop its research programme in epidemiology.

Dr Gilliam's assignment is part of a programme to strengthen the teaching staff of the Institute of Hygiene through an exchange of faculty members of the Institute and the Johns Hopkins University School of Hygiene and Public Health. The Rockefeller Foundation is a co-sponsor of this project, which was started with WHO assistance in 1953.

Dr Gilliam obtained his Bachelor of Science degree and his Doctorate in Medicine from the University of Virginia and his Doctorate in Public Health (Epidemiology) from Johns Hopkins University. From 1934 to 1960, he served as head of the epidemiological section, National Cancer Institute, US Public Health Service. He joined the teaching staff of Johns Hopkins University in 1960.

Post-basic nursing in Denmark

Miss Elizabeth Logan, Associate Professor of Nursing, School for Graduate Nurses, McGill University, Montreal, Canada, has been appointed by WHO as short-term consultant to the Nursing Division of the National Health Service of Denmark. Miss Logan will advise on new post-basic nursing programmes and help the staff of the post-basic nursing school of the University of Aarhus in the application of the revised programmes and the reorganization of

the school. She will also help the school and agencies receiving the students for practical work to arrange for facilities for clinical and public health training under the revised programmes.

Miss Logan obtained her B.Sc. degree at the Acadia University, Wolfville, Nova Scotia, and her Master's degree in nursing at the Yale University School of Nursing, New Haven, Conn.

Appointment of new Assistant Director-General

Dr Oganes Vagarshakovich Baroyan, of the USSR, has been appointed Assistant Director-General of WHO, and will be personally responsible for the Divisions of Health Statistics, Biology and Pharmacology, and Editorial and Reference Services. As one of the four Assistant Directors-General of WHO, he will advise the Director-General on major questions of policy.

Born in Erevan, Soviet Armenia, in 1906 and educated at the first Moscow Medical Institute, Dr Baroyan comes to Geneva from Moscow, where he has been directing the Gamaleya Institute of Epidemiology and Microbiology. This institute is one of the oldest in the USSR; it started as a small laboratory some 50 years ago, but since the revolution and particularly from 1935 onwards it has incorporated many laboratories and other institutes and is now the largest institute in the USSR working in the fields of immunology, epidemiology, and microbiology. It contains over 20 departments and laboratories and has 1700 staff members, including 315 scientists.

Since 1951, Dr Baroyan has also held the post of Director of the Epidemiology Department and Professor of Epidemiology of the Ivanovsky Virology Institute. From 1943 to 1947, he was Plenipotentiary Representative of the Red Cross in Eastern Countries and from 1939 he was Deputy Minister of Public Health of the Dagestan ASSR. He has had wide experience in the fields of epidemiology and public health and in the course of his career has visited China, Ethiopia, and Iran. Dr Baroyan has published numerous scientific papers and monographs in the field of epidemiology; he is a Corresponding Member of the Academy of Sciences of the USSR.

Review of WHO Publications

Joint ILO/WHO Committee on the Hygiene of Seafarers: Third Report (*World Health Organization Technical Report Series*, No. 224), Geneva, 1961, 14 pages. Price: 1/9, $0.30, or Sw. fr. 1.

A Joint ILO/WHO Committee on the Hygiene of Seafarers [1] reviews in this report the nature and extent of the health problems of seafarers, the health services currently available to them, and methods of expanding and improving these services. Medical examinations of seamen, health centres and other port facilities for their care, and provisions for care on board ship when there is no ship's surgeon are considered in the light of ILO Conventions and Recommendations dating as far back as 1921 and the proposal of a WHO consultant [2] for the establishment of health centres for seafarers.

The report lays down the lines along which future efforts should develop, especially in co-ordinating existing facilities so as to avoid duplication of services and fill the gaps still to be found in them.

[1] Members of the Committee: Dr D. Choudhury, India; Mr P. de Vries, United Kingdom; Dr L. R. Hirtle, Canada (Chairman); Dr J. Lembrez, France (Rapporteur); Captain O. I. Loennechen, Norway; Mr J. Scott, United Kingdom (Vice-Chairman); Sir Richard Snedden, United Kingdom (Rapporteur) (assisted by Dr A. L. Hadley, United Kingdom); Dr E. Werner, Sweden. Secretariat: Mr T. Bratt, ILO (Joint Secretary); Dr A. Hutchison (Consultant); Dr M. O. Shoib, WHO (Joint Secretary).

[2] See *WHO Chronicle*, 1961, **15**, 371.

Expert Committee on the Public Health Aspects of Housing: First Report (*World Health Organization Technical Report Series*, No. 225), Geneva, 1961, 60 pages. Price: 3/6, $0.60 or Sw. fr. 2.

The World Health Organization recently convened a meeting of experts representative of several different nations to discuss, from the public health point of view, the improvement of housing and the promotion of urban and rural development. The report of this expert committee [1] identifies housing as a complex process involving many different disciplines, and it will be of interest not only to public health officers and sanitary engineers, but also to town and country planners, architects, building engineers, sociologists, and many others whose services are needed in the task of improving living conditions.

After a brief general review of the subject, which includes a discussion of housing standards, the relationship between housing and health, and world housing conditions, the report sets forth the criteria for a healthful residential environment, taking into consideration the design and layout of individual dwellings; water supply and sewage disposal systems; domestic facilities; physiological requirements affected by such environmental factors as temperature, humidity, ventilation and illumination; protection from fire and other hazards; and community planning.

[1] Members of the Committee: Mr A. L. Berti, Venezuela; Mr G. Blachère, France (Vice-Chairman); Mr H. von Hertzen, Finland; Mr E. Lartey, Ghana; Dr Y. D. Lebedev, USSR, Dr J. M. Mackintosh, United Kingdom (Chairman); Mr N. V. Modak, India; Dr C. Woodbury, USA (Rapporteur). Representatives of the United Nations: Mr E. Weissmann; Mr A. Turin. Secretariat: Dr H. G. Baity, WHO; Mr R. N. Clark, WHO; Dr G. Lambert, France (Consultant); Mr J. N. Lanoix, WHO (Secretary); Mr E. W. Mood, USA (Consultant).

Over the years, the housing shortage in cities has sometimes led to a neglect of the countrysides In fact, rural housing may be so defective that the population is induced to move to the town. in search of habitations which, although often overcrowded and in slum areas, are preferable to the substandard rural dwellings formerly occupied. The report notes the problems peculiar to rural housing and suggests some of the ways in which they can be overcome. Another special topic dealt with is housing for the elderly and the handicapped, in particular the services and facilities needed to meet the physiological and psychological requirements of these groups.

The report continues with an examination of the obligations of public health agencies in the provision of safe and sanitary housing, and their legal functions in the protection of the residential environment. The part that public health workers can play as community developers is underlined, and the training of these and other technical personnel in the field of housing and community planning is discussed.

Finally, the report enumerates some of the areas in which research is needed and makes suggestions for future action, such as the formation of national committees for housing and health and the establishment of housing programmes within central public health agencies.

Diagnosis and Treatment of Acute Radiation Injury: Proceedings of a Scientific Meeting jointly sponsored by the International Atomic Energy Agency and the World Health Organization, Geneva, 1961, 425 pages. Price: £2, $8.00, or Sw. fr. 24.—.

This publication is discussed in the articles starting on pages 445 and 461.

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